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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61J 1/00

A1

(11) International Publication Number: **WO 97/25015**

(43) International Publication Date: 17 July 1997 (17.07.97)

(21) International Application Number: PCT/CA97/00017

(22) International Filing Date: 10 January 1997 (10.01.97)

(30) Priority Data:
08/584,049 11 January 1996 (11.01.96) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/584,049 (CIP)
Filed on 11 January 1996 (11.01.96)

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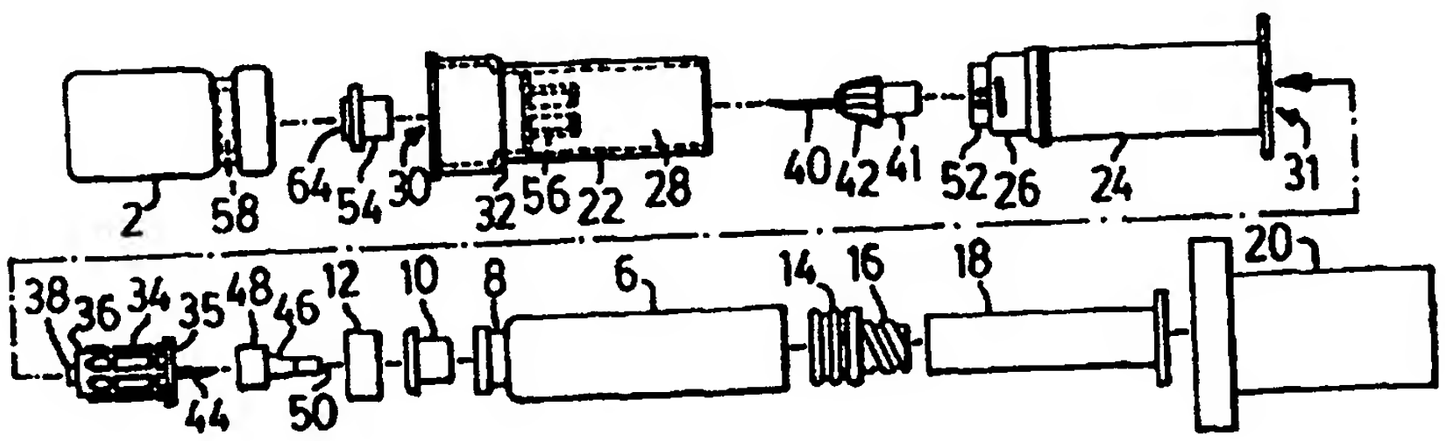
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DELIVERY SYSTEM FOR PHARMACEUTICALS PACKED IN PHARMACEUTICAL VIALS



(57) Abstract

A system is provided for providing syringes filled with pharmaceuticals whose components must be stored separately, using an active ingredient in a pharmaceutical vial (2), a diluent in a protosyringe such as a bottomless vial (4) or a cartridge, and a combiner assembly which enables the content of the pharmaceutical vial to be transferred into the protosyringe and converts it into a ready-to-use syringe on activation. The combined assembly included a tubular body (22, 24) having recesses (30, 31) at opposite ends for receiving capped ends of the vial (2) and the protosyringe (4), and a hub (34) and needle (40, 44) assembly between penetrable sheaths or shields (46, 64) which acts on activation of the assembly to enable the transfer and conversion referred to above. Components of the system may also be used to convert protosyringes and pharmaceutical vials containing pharmaceuticals into delivery systems.

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DELIVERY SYSTEM FOR PHARMACEUTICALS PACKED IN PHARMACEUTICAL VIALS

This invention relates to delivery systems for multiple component pharmaceutical preparations.

Many pharmaceutical preparations must be distributed as two or more separate components which can only be combined shortly before administration of the preparation, usually because the combined preparation is subject to rapid deterioration or otherwise unstable, and the components are only stable when stored separately. Typically at least one component of such a preparation is a liquid which acts as a solvent, diluent or carrier for the other component.

Traditionally such preparations have been prepared shortly before administration by taking one component packaged in a conventional pharmaceutical vial having a neck closed by a penetrable elastomeric stopper secured to a neck of the vial by a cap, taking a second liquid component in a hypodermic syringe, injecting the second component into the vial through the stopper, swilling the vial impaled on the syringe to dissolve, dilute or suspend the first component in the second component, and aspirating the combined components back into the syringe by withdrawing its plunger. This procedure requires a degree of dexterity, is subject to the errors commonly associated with manual on-site preparation of pharmaceuticals, and may compromise sterility. If a third component is used, the procedure must be repeated.

In endeavours to overcome these problems, many proposals have been made for systems to provide prepackaged two component pharmaceuticals, but these tend to suffer from one or more problems of their own such as complex and expensive structure requirements for specialized filling

equipment, complex manipulation at the time of use, and often most serious of all, a heavy burden in time and expense in obtaining regulatory approval for a new product.

U.S. Patent No. 3,872,867 (Killinger) utilizes a tubular assembly incorporating a double ended cannula, into which two pharmaceutical vials are pressed in order to combine components in the two vials. The system requires that one of the vials is under vacuum at pressure, and merely results in a vial containing the combined product, which must still be transferred to a syringe for administration.

U.S. Patent No. 3,563,373 (Paulson) discloses an arrangement utilizing two cartridges in tandem for packaging a two component pharmaceutical, utilizing an intermediate assembly incorporating a double ended needle, which penetrates the piston of one cartridge and neck stopper of the other. The arrangement cannot utilize a standard pharmaceutical vial.

U.S. Patent No. 4,060,082 (Lindberg) also requires two syringes in tandem for combining a two component pharmaceutical, as well as specialized auxiliary pistons in the syringes.

U.S. Patent No. 4,583,971 (Bocquet et al) discloses apparatus for transferring liquid through a cannula from a flexible container to dissolve a pharmaceutical, and returning the solution to the flexible container. The system is dependent upon manipulation of a tangible closure through the flexible container and could not be used to transfer liquid from a syringe to a pharmaceutical vial and back again.

U.S. Patent No. 5,171,214 (Kolber et al) discloses a combination of a vial assembly, a syringe assembly, and an adapter for attaching the vial assembly to the syringe assembly so that a liquid constituent may be transferred from the syringe to the vial and the admixed compounds returned to the syringe. A special vial and special syringe are required, and indeed the system is predicated upon the use of a proprietary vial assembly.

An object of the present invention is to provide a delivery system for two component pharmaceuticals which is economical to manufacture, easy to manipulate, and can minimize regulatory burdens.

SUMMARY OF THE INVENTION

According to the invention, there is provided an activation assembly for a protosyringe or pharmaceutical vial having a penetrable septum, comprising a tubular socket having a first portion extending from an open end to receive in said open end at least a portion of a protosyringe or pharmaceutical vial presenting the penetrable septum, a second portion extending from the first portion to an opposite end of the socket, a guide at said opposite end of the socket, and a hub assembly movable within said guide for movement axially of said second portion of the socket, the hub assembly having a cannula extending into the socket at one end thereof from a liquid delivery conduit at the other end thereof, and a penetrable sheath enclosing the cannula, the hub and the protosyringe or pharmaceutical vial being relatively movable within the socket between a position in which the shield contacts the penetrable septum in a zone coaxial with the cannula, and a position in which the cannula penetrates both the shield and the septum.

The invention extends to an assembly for preparing a prefilled syringe from separately prepackaged components of a multi-component pharmaceutical preparation, the assembly comprising a two part tubular body; the body defining in a first part a first cylindrical recess at one end of a diameter to receive, as a sliding fit, a capped end of a protosyringe at which end a cap retains a penetrable closure on a neck of the protosyringe, as well as a substantial portion of a cylindrical body of the protosyringe, the cylindrical body containing a first, liquid component of the pharmaceutical preparation, retained in the body by a piston within the cylindrical body and forming a hermetic sliding seal therewith; a second cylindrical recess defined in the other end of the tubular body by a second detachable part to receive as a press fit a cap securing a penetrable closure at the neck of a pharmaceutical vial containing a second component of the pharmaceutical preparation; the tubular body defining in said first part a passage connecting the cylindrical recesses; a hub movable longitudinally of the tubular body within the passage; cannulas extending longitudinally of the tubular body from said hub to distal ends in opposite directions and communicating with one another through said hub; penetrable shield members covering the distal ends of the cannulas and located to contact penetrable closures of a protosyringe and of a pharmaceutical vial inserted in the cylindrical recesses; and a hollow cylindrical overcap concentric with the hub assembly and located within the tubular body in the first cylindrical recess, the overcap being connected to the hub to limit movement of the latter into the passage; the depth of the cylindrical recess, the length of the passage connecting the recesses, the extent of the cannulas from the hub, and the location of the overcap in the first cylindrical recess, being such that upon a protosyringe received in the first cylindrical recess and a vial received

in the second recess being driven towards each other, the overcap is driven onto the cap of the protosyringe and the hub moves longitudinally so that the cannulas penetrate both penetrable sealing members and the penetrable closures of the protosyringe and vial respectively to place the protosyringe and vial in fluid communication through the cannulas.

Two terms used in the preceding paragraph and elsewhere in this specification and the appended claims require mention. A 'protosyringe' is an assembly intended to form the basis of a prefilled syringe but requiring the addition of components to form a complete syringe. At minimum, it includes a cylindrical body containing at least a component of a pharmaceutical product, the body being closed at one, necked end by a cap securing a penetrable closure and at an opposite open end by a piston connected to or provided with means for connection to an activating plunger. Protosyringes include bottomless vials as described in my U.S. Patent No. 5,364,369; cartridges; and prefilled syringes requiring at least addition of an overcap as defined below and introduction of a further component of the pharmaceutical product to provide a ready to use syringe. An 'overcap' is a cap adapted to be lodged on the cap of a protosyringe and providing means for supporting a needle or other instrumentality through which contents of a syringe formed from the protosyringe may be discharged. In some instances, a complete prefilled syringe itself may be used as a protosyringe if it has a luer connection closed by a cap of penetrable material over which an overcap may be received.

The invention also extends to the combination of such an assembly with a protosyringe and/or pharmaceutical vials already engaged in their associated cylindrical recesses.

If the protosyringe is already engaged in the first cylindrical recess, its free end may be covered by a removable cap to prevent accidental projection into the cylindrical bottom resulting in premature actuation of the assembly. When a protosyringe or vial is preengaged in its cylindrical recess, the associated sealing member in the assembly is in resilient contact with the penetrable closure of the vial in areas concentric with the cannula so as to help maintain sterility of areas of the sealing members and closures intended to be penetrated by the cannula.

The hub assembly and a modified overcap may also be utilized in conjunction with a protosyringe or pharmaceutical vial to provide alternative delivery systems for pharmaceuticals contained in the protosyringe or vial.

Further features of the invention will be apparent from the following description of embodiments of the invention.

IN THE DRAWINGS

Figure 1 is an exploded view of the components of an assembly according to the invention, including both a protosyringe, in this case a bottomless vial, and a pharmaceutical vial;

Figure 2 illustrates an assembly according to the invention, including a bottomless vial, as it might be shipped;

Figure 3 illustrates a similar assembly, but further including a pharmaceutical vial, ready for activation;

Figure 4 illustrates in part sectional view components of an assembly according to Figure 3, but with upper components removed for clarity;

Figure 5 is a similar view to Figure 4, but showing the illustrated components in the relationship which they assume after activation of the assembly in order to prepare a

completed prefilled syringe;

Figure 6 is a view of the assembly corresponding to Figure 3, after activation;

Figure 7 is a view of the assembly after the plunger has been pressed upwardly to transfer liquid from the bottomless vial to the pharmaceutical vial;

Figure 8 is a view showing a mixing step;

Figure 9 shows upper portions of the assembly being removed, leaving a syringe ready for application of a needle or other discharge means;

Figure 10 shows a partially exploded view of a modified embodiment of delivery system utilizing a different form of protosyringe;

Figures 11 and 12 are fragmentary sectional views of an alternative form of syringe socket and associated parts which permit elements of the delivery system to be used in further embodiments of delivery system in conjunction with prefilled protosyringes or pharmaceutical vials;

Figure 13 shows in section a cap which may be applied to a luer on a hub portion of the embodiment of Figures 11 and 12 to enable the hub to be driven from the position to Figure 11 to that of Figure 12 to activate a prefilled protosyringe;

Figure 14 shows in an exploded view parts of an alternative activation system for use with the embodiment of Figures 11 and 12 so as to activate a syringe or vial for use in conjunction with a standard flexible mini-bag;

Figure 15 shows an assembled syringe ready for activation;

Figure 16 shows an activated syringe applied to a mini-bag;

Figure 17 is an exploded view illustrating components of a presently preferred modification of the embodiment of Figures 1-9;

Figure 18 shows the parts shown in Figure 17 assembled

ready for use, less the plunger;

Figures 19 and 20 illustrate a presently preferred modification of the embodiment of Figures 11 and 12;

Figure 21 illustrates the assembled components of a further embodiment of assembly according to the invention;

Figure 22 is an exploded view of components of a hub assembly used in the embodiment of Figure 21;

Figure 23 illustrates a modification of the embodiment of Figure 18, showing how the assembly of the invention may be used to activate pharmaceuticals having more than two components;

Figure 24 illustrates an assembly in accordance with a further embodiment of the invention; and

Figure 25 is a flow diagram illustrating the preparation of assemblies in accordance with the embodiment of Figures 17 and 18.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring first to Figures 1 to 3, the parts are shown of an assembly for preparing a syringe containing a pharmaceutical preparation, components A and B of which are contained respectively in a pharmaceutical vial 2 and a protosyringe in the form of a bottomless vial 4 consisting of a cylindrical body 6, open at one end and provided with a neck 8 at its other end, the neck being closed by an elastomeric closure 10 secured in place by a metal cap 12 crimped over the neck. A piston 14 is lodged in the open end of the body, the piston being provided with means 16 by which a detachable plunger 18 may be secured to the piston. The plunger will normally be shipped detached from the piston, both to reduce the overall length of the assembly, and to permit a removable cap 20 to be applied over a projecting end of the bottomless vial 4 as shown in Figure 2 so as to prevent inadvertent premature activation of the assembly.

At least one of the components A and B is liquid; usually it will be convenient to locate a liquid component in the bottomless vial but it would be possible to locate a solid component in the bottomless vial provided that the latter also contains an air or gas volume sufficient to displace liquid contents of the vial 2.

Since a typical two component pharmaceutical for administration via a syringe comprises an active ingredient and a liquid solvent, diluent or carrier (hereinafter collectively referred to as diluent for convenience) which in the majority of cases will be one of only a few different types (most usually distilled water), it will usually be advantageous to place the active component in the vial 2; this is because in many, if not most cases, a suitable vial package of the active ingredient will already be certified by regulatory authorities, or need in any event to be so certified, while certification of the protosyringe containing the diluent will generally be straightforward if the diluent is conventional and the protosyringe structure itself is already certified. The transfer assembly will be generic and can be separately certified; accordingly combinations of pharmaceutical components and assemblies for converting them into filled syringes can be assembled from separately certified components with little if any need for certification of the combination.

A main portion of the assembly has a tubular body formed by two components, a vial coupling 22 and a syringe socket 24. The syringe socket 24 has an externally threaded end portion 26 at one end which screws into an internal thread 28 at an adjacent end of the vial coupling 22. The vial coupling provides a cylindrical recess 30 to receive a capped end of the vial 2, whose degree of insertion is limited by a shoulder 32. The syringe socket 24 provides a

cylindrical recess 31 into which may be slid the body 6 of the bottomless vial 4, although not initially to the full extent permitted by the depth of the recess.

The end portion 26 of the syringe socket includes a guide 52 for longitudinal movement of a hub 34, formed at a front end with a liquid delivery conduit through a standard luer as utilized in the industry for coupling needles, or other delivery instrumentalities forming liquid delivery conduit extensions, to syringes and other sources of liquid pharmaceuticals. Such a luer comprises an internally threaded socket 36 for locking a needle in place, and a tapered central spigot 38 for establishing a seal with a complementary socket on the needle. In the present instance, a hollow transfer needle 40 has a socket 41 lodged on the central spigot, but is not provided with threads to engage those of the socket 36, so the needle 40 may be pulled from the spigot 38. A tapered shoulder 42 is formed on the transfer needle 40. The hub 34 has a hollow needle or cannula 44 projecting from its end opposite the spigot 38 and in communication with a central passage in the spigot. A flexible needle sheath or shield 46 of thin rubber covers the needle 44, having a portion 48 engaging a socket in the end of the hub 34, and a flattened end 50 over the free end of the needle. Internally of the guide 52, the end portion 26 of the syringe socket also contains an extension of the cylindrical recess 31 dimensioned to provide an overcap which is a press fit over the cap 12 of the bottomless vial 4.

The vial coupling 22 has a passage extending from the recess 30 which receives the vial 2 to its internally threaded end, the passage being closed by a rubber stopper or shield 54. Between the rubber stopper and the internally threaded end of the coupling 22, the passage is formed

internally with resilient pawls 56 which will detain the shoulder 42 of the needle 40 when the latter is pressed past the pawls.

The assembly just described may be shipped on its own with neither vial installed, in which case a removable cover (not shown) will be required to cover the cylindrical recess in the coupling 22 to maintain sterility, or with one or both vials installed (see Figures 2 and 3). When a vial 2 is installed, any removable central portion of a cap 60 covering a penetrable closure 58 of the vial is flipped off, so that the penetrable closure may contact a rib 64 on the stopper 54 to enclose an axial sterile zone of the two rubber parts 58 and 54. Likewise, an axial zone of the closure 10, similarly exposed, contacts the end 50 of the needle sheath 46 to provide protected zones on the contacting rubber parts.

In order to activate the assembly, after installation of the vials to provide the arrangement shown in Figure 3, the bottomless vial is pressed into the syringe socket 24, and the plunger 18 is attached to reach the condition shown in Figure 6.

Thereafter, the assembly is inverted and plunger 18 is activated to project the liquid content B from the bottomless vial into the pharmaceutical vial, (see Figure 7), the assembly then being swilled as shown in Figure 8 to dissolve, mix or suspend the contents of the vial 2 in the liquid, which is then aspirated back into the bottomless vial by withdrawing the plunger to reach a condition similar to that of Figure 6, except that component A is now incorporated into component B to leave a product C in the bottomless vial. The vial 22 is now unscrewed from the syringe socket 24 and withdrawn, taking with it the transfer

needle 40 which is pulled off the spigot 38 by the pawls 56, thus leaving the luer of hub 34 ready to receive a needle or other fluid connection instrumentality, and providing a completed ready to use syringe, filled with the two component pharmaceutical (see Figure 9). The hub 34 is retained on the cap 12 of the bottomless vial by the syringe socket 24, with the needle providing a passage between the body 6 and the luer 36, 38.

If the initial position of liquid and solid components is reversed, the step of Figure 7 may be performed without inversion, with reciprocation of the syringe plunger being used to force air or gas from the vial 4 to the vial 2, and liquid from the vial 2 to the vial 4.

A presently preferred modification of the assembly described above is shown in Figures 17 and 18, in which the same reference numerals are used to designate similar parts, and only the differences are described. In this modification, the flange 35 of the hub 34 is extended to form the overcap, and the portion 26 of the syringe socket 24 acts to receive the forward portion of this overcap when the syringe body 6 is forced forward against and into the overcap during activation of the syringe. As best understood from Figure 25, this rearrangement facilitates assembly. The cap 20 is replaced by a driver 21, which snaps into the opening of the syringe socket 24 as shown in Figure 18 in a position in which it covers the rear of the protosyringe, and from which position it can be driven forward to activate the assembly. The driver 21 has a bottom aperture to accommodate the plunger 18. The stopper 54 is replaced by a flexible sheath 54 similar to the shield 46, since this is found to simplify assembly and provides complete coverage of the needle 40.

Various modifications are possible within the scope of the invention, the above description being of a presently preferred example. For instance, the needle 40 could be permanently secured to the hub 34, and the pawls in the vial omitted. Such an arrangement does not provide the user with any choice as to the needle to be used on the finished syringe, and needle length may be severely limited by the need to avoid excess needle extent to the vial 2, which would make it difficult to aspirate its contents.

Likewise, the bottomless vial 4 may be replaced by other forms of protosyringe such as cartridges, or by a prefilled syringe provided with an elastomeric closure covering a luer connection, the front end of the syringe accepting an overcap providing such a needle connection and acting to retain the hub. Such an arrangement is exemplified in Figure 10, which shows the bottomless vial replaced by a protosyringe which is a conventional prefilled syringe having a conventional luer nozzle 101 protected by a protective rubber sealing cap 100 over a front end of the syringe body, and the syringe socket 24 is modified in shape to receive the body 6 of the syringe, with longitudinal internal ribs 102 to grip the syringe body. As before, a cap 20 prevents the syringe body from being driven fully into the syringe socket 24 until activation is required, and the end 50 of the shield 46 rests against the cap 100 to help maintain sterility of the zones to be penetrated by the needle 44.

Yet further forms of protosyringe may be employed. For example, a known form of diluent vial comprises a body 6 in the form of a glass tube with a piston at both ends. The piston at one end is similar to the piston 14 with an extension similar to the extension 16. The piston at the other end fulfills the function of the neck 8, stopper

10 and cap 12 of the bottomless vial shown in Figure 1. In conventional use, this other end of the vial is inserted into an open end of a sleeve which at its other end supports a luer or needle externally and an axial hollow pin projecting internally. The piston at the other end of the vial has an axial passage, through the piston and an outward extension of the piston, closed at its outer end by a bung which is displaced by the hollow pin on insertion of the vial into the sleeve, thus establishing communication between the needle or luer and the interior of the vial. Protosyringe from a vial into a syringe is completed by applying a plunger ot the piston at the first end. This type of protosyringe can be substituted in the present invention for that shown in Figure 1 or Figure 17. During activation, the overcap 16 or 35 will be driven into the extension of the piston at said other end of the vial so that the needle 44 penetrates the sheath 46 and displaces the bung. The bung may be replaced by an integral septum in the passage of the piston which is penetrated by the needle 44.

The syringe socket itself may be made detachable from the completed syringe except for the overcap, or may be truncated in length as shown in Figures 11 and 12. It will be seen that the syringe socket 24 is shortened and reduced in diameter to receive the cap 12 of a bottomless vial, the syringe socket being pushed down over the cap 12 to engage the shoulder of the syringe body 6.

On activation of the syringe the hub 34 is driven downwardly relative to the end portion 26 of the socket 24 from the position shown in Figure 11 to the position shown in Figure 12. In the position shown in Figure 11, the end 50 of the rubber shield 46 rests against the closure 10 so as to provide a protected contact zone, which is penetrated

by the needle 44 on the hub 34 as the hub is driv n downwardly through the guide 52 until a flange 35 on the bottom of the hub 34 contacts the closure 10. At this point the needle 44 establishes communication with the interior of the body 6 of the protosyringe.

Figure 21 shows how the arrangement of Figures 11 and 12 (or Figures 19 and 20 considered below) may be used in an arrangement in which the assembly is activated by insertion of the vial 2. As best seen in Figure 22, the component 42 is lengthened and modified so that it, the penetrable shield 54 on the cannula 40, and the cannula 40 itself, project into the vial socket 32. On insertion of the vial 2, the shield 54 is pressed into a recess in the arrangement 42 so that it is penetrated by the cannula, which also penetrates the closure of the vial 2, and the vial closure presses on the component 42 so as to drive the cannula 44 through its sheath or shield and the penetrable closure of the protosyringe. If the modification of Figures 19 and 20 is used, with a hub 34 modified as shown in Figure 22 so that the flange 35 provides the overcap, this driving action also drives the overcap 35 onto the cap of the protosyringe. If the arrangement of Figures 11 and 12 is used, the cap of the protosyringe is already lodged in the overcap.

Figure 13 illustrates an alternative means of driving the hub 34. The luer spigot 38 of the hub 34 is covered by a conventional moulded cover 104, shown in section in Figure 13, screwed into the socket 36 and providing a convenient driver for the hub which can be unscrewed and discarded preparatory to fitting a needle to the luer of the hub.

Figures 14 and 15 illustrate an alternative driver arrangement, making use of a known type of adapter used to couple syringes to flexible mini-bags so that the contents

of the syringe may be discharged into the bag and mixed with the contents of the latter. The adapter 106 consists of a tube 108 which has an internally threaded socket 118 at one end for screwing in the present case on to complementary external threads on the portion 26 of a syringe socket 24, and slots 110 at the other end to engage lugs on a nipple of the bag so that the nipple is guided into the adapter concentrically aligned with a needle 112 fitted to the spigot 38 of the hub 34. A cap 114 covers the slotted end of the tube 108, and has a concentric internal tubular extension 116 that sheathes the needle 112, and extends the socket 36 of the hub 34 when the latter is in the position shown in Figure 11, with the tube 108 extending only part way into the cap 114. Pushing further on the cap will force the hub 34 from the position shown in Figure 11 to the position shown in Figure 12, thus activating the syringe. The cap 114 may then be removed, and the syringe applied to a mini-bag as shown in Figure 16. Alternatively the tube 10 may also be removed providing a ready to use syringe.

Instead of a protosyringe in the form of a bottomless vial, the arrangement of Figures 11, 12, 14 and 15 may also be used to activate a regular pharmaceutical vial so that its contents may be mixed with those of a mini-bag or other flexible bag. Liquid from the flexible bag may be caused to enter the activated vial through the needle, and the admixed contents of the vial then allowed to run back into the bag through the needle by suitable manipulation of the bag and the attached activated vial.

The arrangement shown in Figures 11 and 12 may also be modified as shown in Figures 19 and 20 by extending the flange 35 of the hub 34 to form the overcap (see also Figure 22). In order to accommodate downward movement of the overcap while preventing inward movement of the

protosyringe, the reduced diameter portion of the syringe socket is extended downward as at 27 to form a shoulder limiting insertion of the protosyringe.

Figure 23 shows a modification of the embodiment of Figures 17 and 18 to allow preparation of a three component pharmaceutical. The vial socket 22 is bifurcated, as is the component 42, so as to provide two vial sockets 30, and two needles which are not seen since they are covered by sheaths 54. On activation of the assembly by driving the driver 21 into the syringe socket 24, the closures of the vials will be penetrated simultaneously, enabling liquid from the protosyringe body 6 to enter both vials 2 and dissolve or suspend their contents. On activation, latch members 56 engage the component 42 to retain it, as in previous embodiments.

A further vial socket 30 and a further branch of the component 42 may be provided for each additional component to be handled.

Referring now to Figure 24, the principles of the invention may also be utilized with protosyringes in the form of a shell vial (or as shown, the functional equivalent of a shell vial produced by reversing a bottomless vial 206 as described in U.S. 5,364,369A and applying a driver cap 220 to its cap end). Such shell vials are normally formed into a completed syringe by screwing a threaded extension 216 of a piston 214 into a free end of a plunger stem within a concentric syringe shell connected to the other end of the plunger. A double ended needle extends axially of the plunger stem and out of its other end. Screwing the extension 216 fully onto the plunger stem causes the needle to penetrate the piston so that the contents of the shell vial may be expelled through the needle by driving the vial

onto the plunger stem. Such an arrangement is described in US 5,171,214A already referenced above. In the present instance, a syringe socket 224 provides the shell, and the hub assembly utilized in the embodiment of Figures 1-10, modified as shown in Figures 17 and 18, is further modified by providing an elongated cannula 244 surrounded by a concentric plunger stem 218 positioned on the cannula by passing through a flange 245 and entering the overcap 35. The length of the cannula 244 is such that it ends short of a penetrable septum (not shown) within the piston 21 with the components in the unactivated state shown in Figure 24, with the piston extension 216 screwed into a threaded socket at the bottom of stem 218.

The assembly is activated by driving the shell vial upwardly so that a reduced diameter portion 219 of the stem 228 enters the overcap 35, permitting the cannula 244 to perforate the septum in the piston. Further upward movement causes the cannula supported at the upper end of the hub to penetrate the sheath 64 and the penetrable closure of the vial 2, whereafter activation can proceed as previously described save that the shell vial 206 is manipulated in place of a conventional plunger.

Referring now to Figure 25, there is shown a flow diagram of the preparation of an assembly in accordance with the invention, specifically the embodiment of Figures 17 and 18.

Starting at the top left, the parts 34, 35, 42, 46 and 64 are assembled to form the hub assembly 300, which is then sterilized by gamma radiation (step 32°). Within a clean room 314 (top right) the parts 6, 12, 14, 16 are assembled and filled to provide a protosyringe 304 to the cap of which the overcap 35 is applied, but not far enough for the

cannula within the overcap 35 to penetrate the shield or sheath 46, to provide subassembly 306, which then passes through an inspection station 316.

In the meanwhile parts 21, 22 and 24 are assembled to provide a subassembly 302 and, together with the plunger 18, sterilized by gamma radiation at 322. The assembly 306 of protosyringe and hub assembly is inserted into the assembly 302 under a laminar flow hood to provide the assembly 308, whereafter, in the same environment, a vial 2, from which any protective metal disc on the cap has been flipped off, is inserted into the vial socket of the assembly 308, which corresponds exactly to that of Figure 18. The contacting surface of the penetrable closure 58 (see Figure 1) of the vial 2 and the surface 50 of the shield 64 are sterilized by a high intensity ultraviolet flash or an antiseptic spray 318 during this step, whereafter the resulting assembly 310 together with the plunger 18 is sealed into a plastic tray 312. The tray is vacuum formed with a recess shaped to correspond to the profile of the assembly 310. In particular, it is advantageous that this recess snugly embraces the narrower portion of the actuator 21 to avoid any possibility of inadvertent activation prior to use occasioned by shock or rough handling.

Variations are of course possible in this procedure. For example, the protosyringe 304 like the vial might be preproduced and terminally sterilized, and assembled to the hub assembly to produce the assembly 306 in a similar manner to combination of assemblies 302 and 308.

CLAIMS:

1. An activation assembly for a protosyringe or pharmaceutical vial having a penetrable septum, comprising a tubular socket having a first portion extending from an open end to receive in said open end at least a portion of a protosyringe or pharmaceutical vial presenting the penetrable septum, a second portion extending from the first portion to an opposite end of the socket, a guide at said opposite end of the socket, and a hub assembly movable within said guide for movement axially of said second portion of the socket, the hub assembly having a cannula extending into the socket at one end thereof from a liquid delivery conduit at the other end thereof, and a penetrable sheath enclosing the cannula, the hub and the protosyringe or pharmaceutical vial being relatively movable within the socket between a position in which the shield contacts the penetrable septum in a zone coaxial with the cannula, and a position in which the cannula penetrates both the shield and the septum.

2. An activation assembly according to Claim 1, wherein the first portion of the socket is of a diameter to receive a body portion of a protosyringe, and the second portion is of a diameter to receive or provide an overcap for the protosyringe upon that portion of the latter presenting the penetrable septum being forced into the overcap, and wherein the hub assembly is position to be projected outwardly through the guide by entry of said portion of a protosyringe into the overcap.

3. An activation assembly according to Claim 1, wherein the first portion of the socket is of a diameter to receive a portion of a vial or protosyringe vial presenting said penetrable septum, and the second portion is of a diameter to receive or provide an overcap for said portion of the

vial or protosyringe, and wherein the hub assembly is positioned to be projected inwardly through the guide and the second portion of the socket to drive the cannula through the shield and the penetrable septum.

4. An activation assembly according to Claim 1, 2 or 3, wherein the liquid delivery conduit comprises a luer.

5. An activation assembly according to Claim 4, wherein the activation assembly comprises a second socket, oppositely directed to the first and having a first portion extending from an open end to receive in said open end a portion of a container having a penetrable septum, and a second portion extending to said guide, the liquid delivery conduit of said hub assembly extending into said second portion of the second socket and including a second cannula detachably mounted on said luer, and a second penetrable shield enclosing the second cannula, the hub assembly and the container being relatively movable within the socket between positions in which the second shield contacts the penetrable septum of the container in a zone coaxial with the cannula, and positions in which the second cannula penetrates the second shield and the second septum.

6. An activation assembly according to Claim 5, wherein the container is a pharmaceutical vial.

7. An activation assembly according to Claim 3, including a driver component to project the hub assembly inwardly through said guide and said second socket portion.

8. An activation assembly according to Claim 7, wherein the liquid delivery conduit is a luer and the driver component is a detachable cap applied to the luer.

9. An activation assembly according to Claim 7, wherein a needle is mounted on the luer, an adapter tube surrounding the needle is attached at one end to the socket and at the other end is shaped to guide a nipple of a flexible bag onto the needle, and a cap is provided which is slidable relative to the other end of the socket and has a tubular extension extending within the adapter or engage the hub assembly and drive the cannula through the closure of a vial whose cap is received in the socket.

10. An activation assembly according to Claim 8, wherein the vial is a bottomless vial.

11. An activation assembly for preparing a prefilled syringe from separately prepackaged components of a multicomponent pharmaceutical preparation, the assembly comprising a two part tubular body; the body defining in a first part a first cylindrical recess at one end of a diameter to receive, as a sliding fit, a capped end of a protosyringe at which end a cap retains a penetrable closure on a neck of the protosyringe, as well as a substantial portion of a cylindrical body of the protosyringe, the cylindrical body containing a first, liquid component of the pharmaceutical preparation, retained in the body by a piston within the cylindrical body and forming a hermetic sliding seal therewith; a second cylindrical recess defined in the other end of the tubular body by a second detachable part to receive as a press fit a cap securing a penetrable closure at the neck of a pharmaceutical vial containing a second component of the pharmaceutical preparation; the tubular body defining in said first part a passage connecting the cylindrical recesses; a hum movable longitudinally of the tubular body within the passage; cannulas extending longitudinally of the tubular body from said hub to distal ends in opposite directions and communicating with one

another through said hub; penetrable shield members covering the distal ends of the cannula and located to contact penetrable drivers of a protosyringe and of a pharmaceutical vial inserted in the cylindrical recesses; and a hollow cylindrical overcap concentric with the hub assembly and located within the tubular body in the first cylindrical recess, the overcap being connected to the hub to limit movement of the latter into the passage; the depth of the cylindrical recess, the length of the passage connecting the recesses, the extent of the cannulas from the hub, and the location of the overcap in the first cylindrical recess, being such that upon a protosyringe received in the first cylindrical recess and a vial received in the second recess being driven towards each other, the overcap is driven onto the cap of the protosyringe and the hub moves longitudinally so that the cannulas penetrate both penetrable sealing members and the penetrable closures of the protosyringe and vial respectively to place the protosyringe and vial in fluid communication through the cannulas.

12. An assembly according to Claim 11, wherein the overcap is integral with said first part of the tubular body.

13. An assembly according to Claim 12, wherein said overcap is integral with the hub.

14. An assembly according to Claim 13, wherein a shoulder is defined in the first recess limiting movement of the cylindrical body of a protosyringe into the first recess such that as to limit its engagement with the overcap to a point where it contacts the sealing member associated with the cannula directed towards the first recess without causing penetration of that sealing member or the penetrable closure of the protosyringe, and a cap of a vial can be pressed far enough into the second recess for the cannula

directed towards that recess to penetrate its associated sealing member and the penetrable closure of the vial, and for the penetrated vial to drive the hub downwards to force the overcap onto the cap of a protosyringe fully inserted in the first recess, and to start the cannula directed towards the first recess through both the sealing member associated therewith and the penetrable closure of the protosyringe.

15. An assembly according to Claim 3, wherein a shoulder is defined in the second recess limiting movement of a cap of a vial into the recess to a location contacting the sealing member associated with that cannula directed towards the second recess without causing penetration of that sealing member or a penetrable closure of the vial, and a cap of a protosyringe can be pressed far enough into the first recess for the cap to enter the overcap far enough that the cannula directed towards the first recess penetrates both the sealing member associated with that cannula and a penetrable closure of the protosyringe and drives the hub sufficiently towards the second recess that the cannula directed towards that recess penetrates both the sealing member associated therewith and a penetrable closure of a vial fully inserted in the second recess.

16. An assembly according to Claim 14, wherein the part of the tubular body defining the second recess includes a detent limiting insertion of a cap of a vial, to a point at which a penetrable closure of the vial contacts the sealing member associated with the cannula directed towards the second recess without resulting in penetration of the sealing member or penetrable closure, until sufficient pressure is applied to the vial to overcome the detent.

17. An assembly according to Claim 15, wherein the overcap includes a detent limiting insertion of a cap of a

protosyringe, to a point at which a penetrable closure of the protosyringe contacts the sealing member associated with the cannula directed towards the first recess without resulting in penetration of the sealing member or penetrable closure, until sufficient pressure is applied to the protosyringe to overcome the detent.

18. An assembly according to Claim 12, wherein the overcap includes a detent limiting insertion of a cap of protosyringe, to a point at which a penetrable closure of the protosyringe contacts the sealing member associated with the cannula directed towards the first recess without resulting in penetration of the sealing member or penetrable closure, until sufficient pressure is applied to the protosyringe to overcome the detent.

19. An assembly according to Claim 11, wherein one end of the cannula, facing a pharmaceutical vial whose cap is installed in the second recess, is separately formed and detachable from the hub assembly and the hub assembly has a luer on which said one end of the cannula is releasably lodged, and means are provided within the detachable part of the tubular assembly to detain within the tubular assembly said one end of the cannula when the cannula is driven into a position penetrating the cap of the pharmaceutical vial.

20. An assembly according to Claim 11, wherein the sealing members are disposed within the assembly so that areas of these members will enter resilient contact with areas of the penetrable closures of a protosyringe and a vial which are concentric with the cannula when the protosyringe and the vial are installed in their respective cylindrical recesses.

21. An assembly according to Claim 11, wherein the body defines, in said second part, plural second cylindrical recesses to receive caps of plural pharmaceutical vials, and said hub comprises plural cannulas extending towards said second cylindrical recesses, and plural sealing members associated with said plural cannulas.

22. An assembly according to Claim 3, wherein the activation assembly comprises a second socket, oppositely directed to the first and having a first portion extending from an open end to receive in said open end an open end of a shell vial closed by a piston having a penetrable septum, and a second portion extending to said guide, the liquid delivery conduit of said hub assembly comprising a cannula.

23. An assembly according to any of Claims 6 or 11 - 22, including a protosyringe and a pharmaceutical vial.

24. A method for producing an assembly according to Claim 6, including two components of a pharmaceutical, at least one of which is liquid, which can be activated to provide a prefilled syringe, comprising producing a sterile protosyringe containing a liquid component of the pharmaceutical, and a sterile pharmaceutical vial containing a second component of the assembly, producing a subassembly comprising said first and second sockets and said guide, producing a hub assembly, sterilizing said subassembly and said hub assembly, and inserting said assembly and said protosyringe into said first socket and said vial into said second socket while maintaining sterility at the zones of contact of the shields with the penetrable septums.

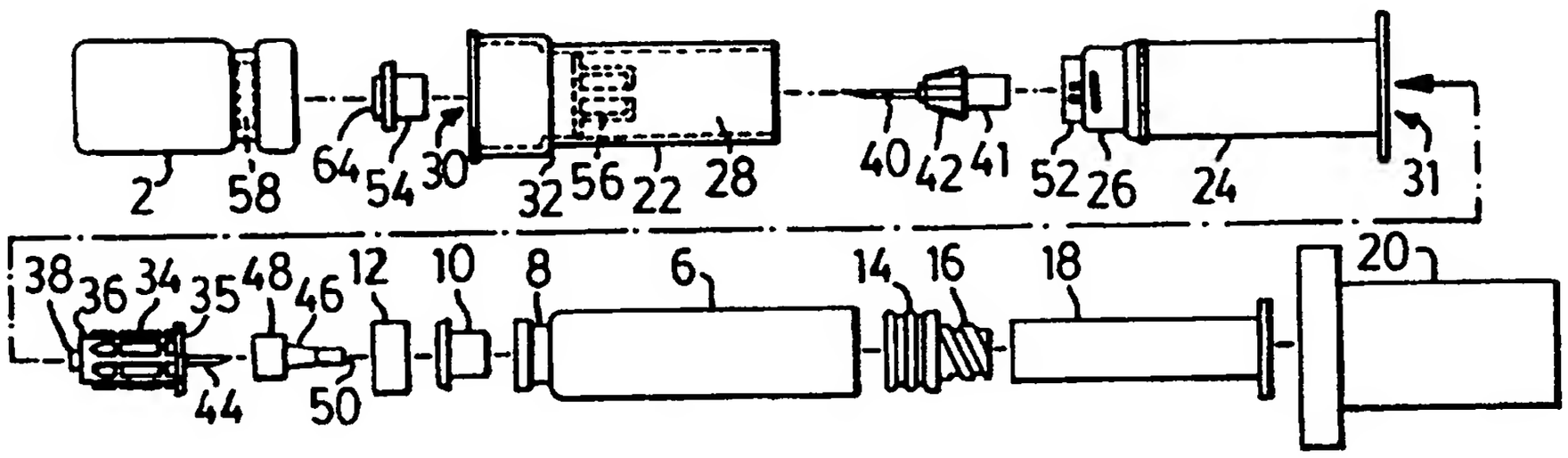

FIG.1

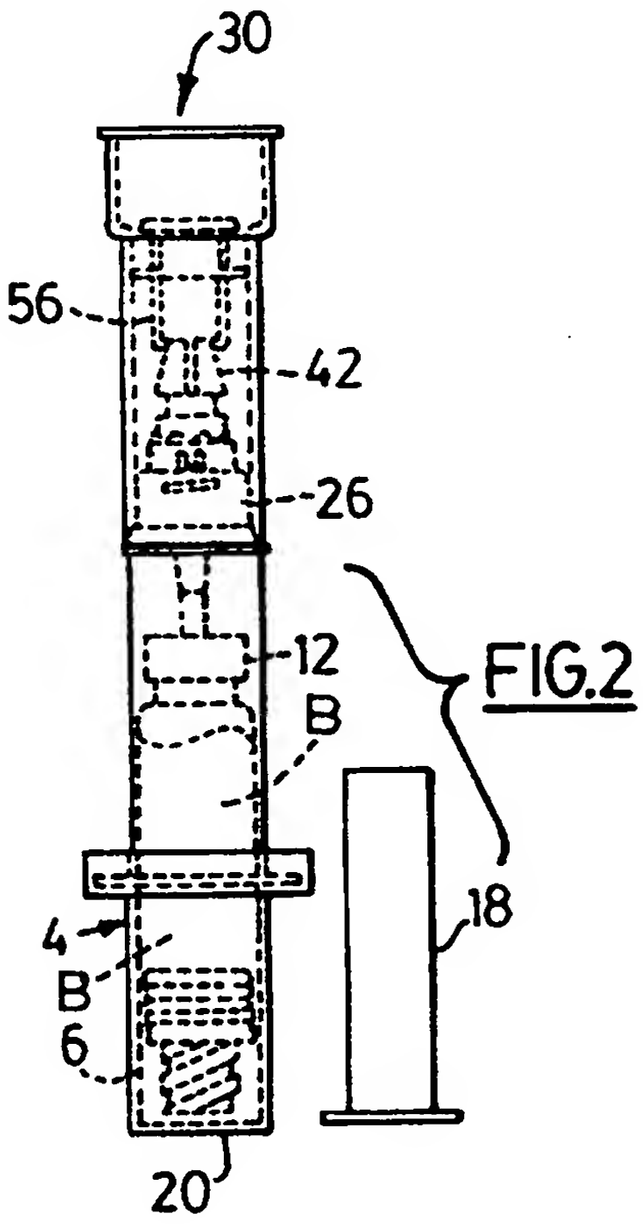

FIG.2

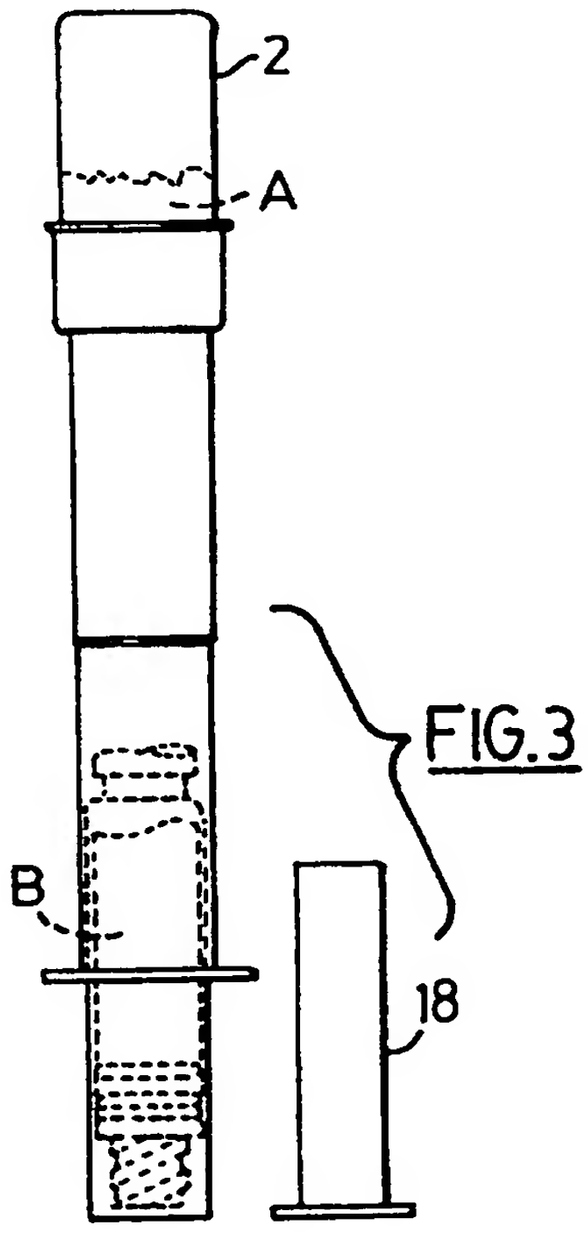

FIG.3

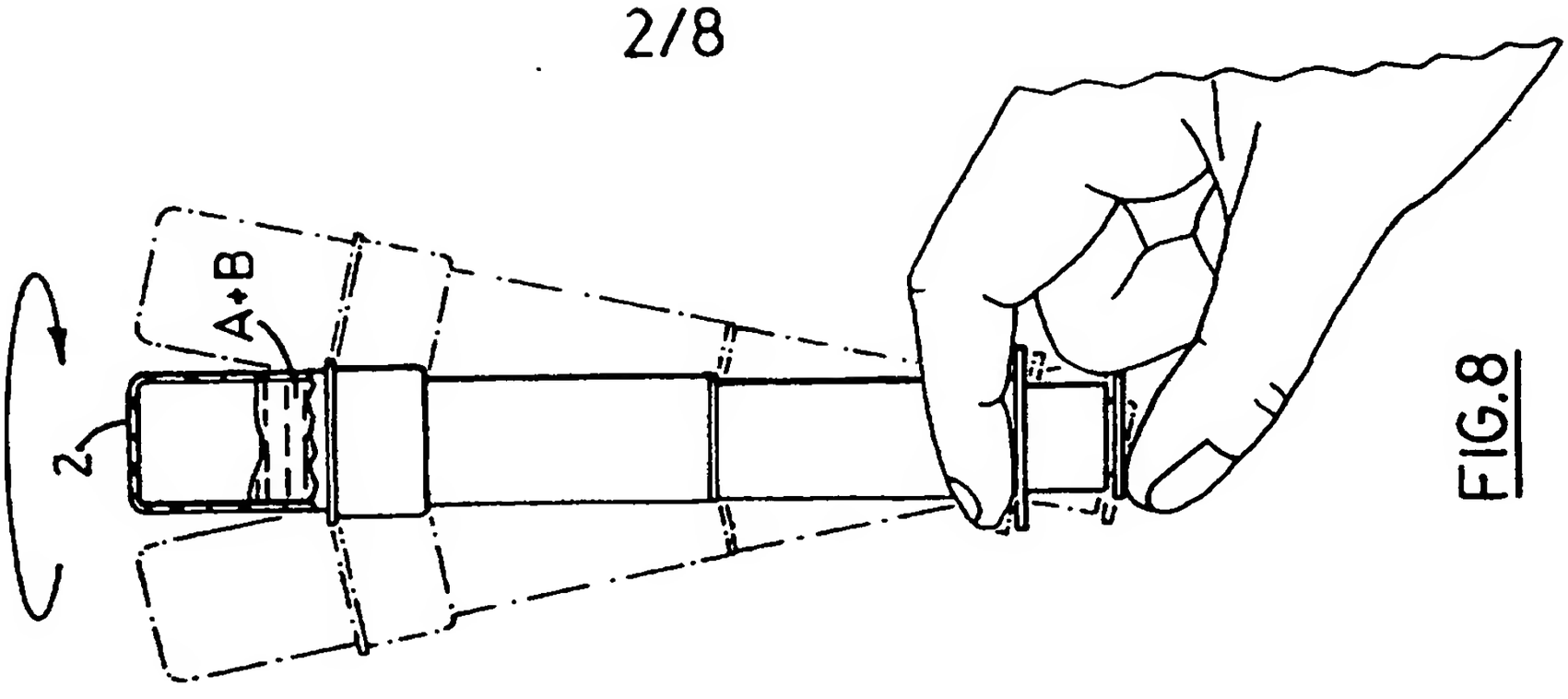

FIG.8

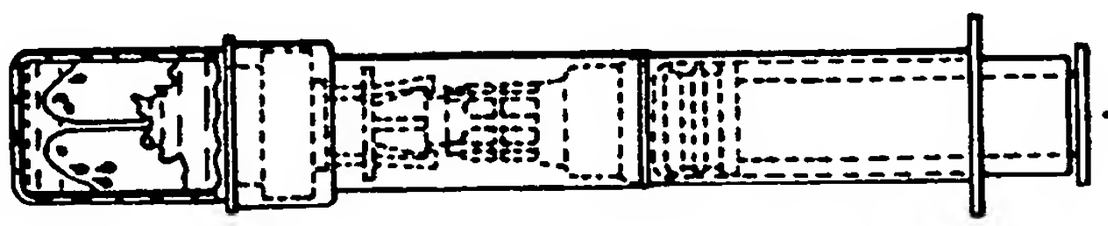

FIG.7

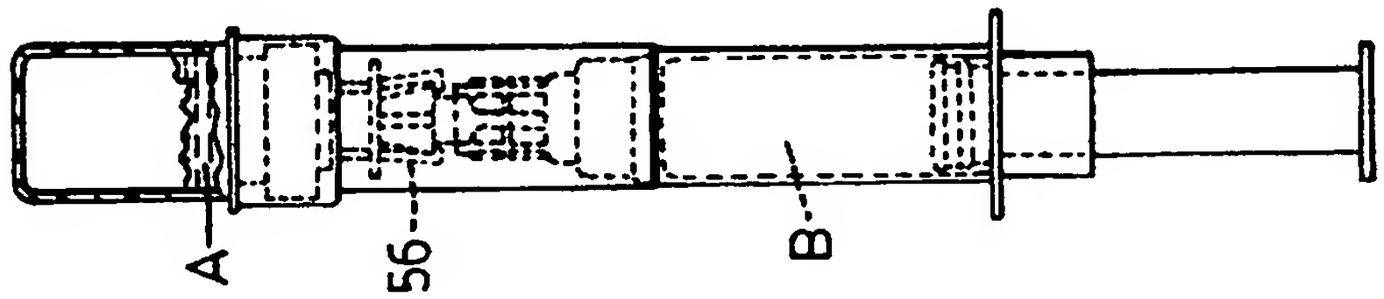

FIG.6

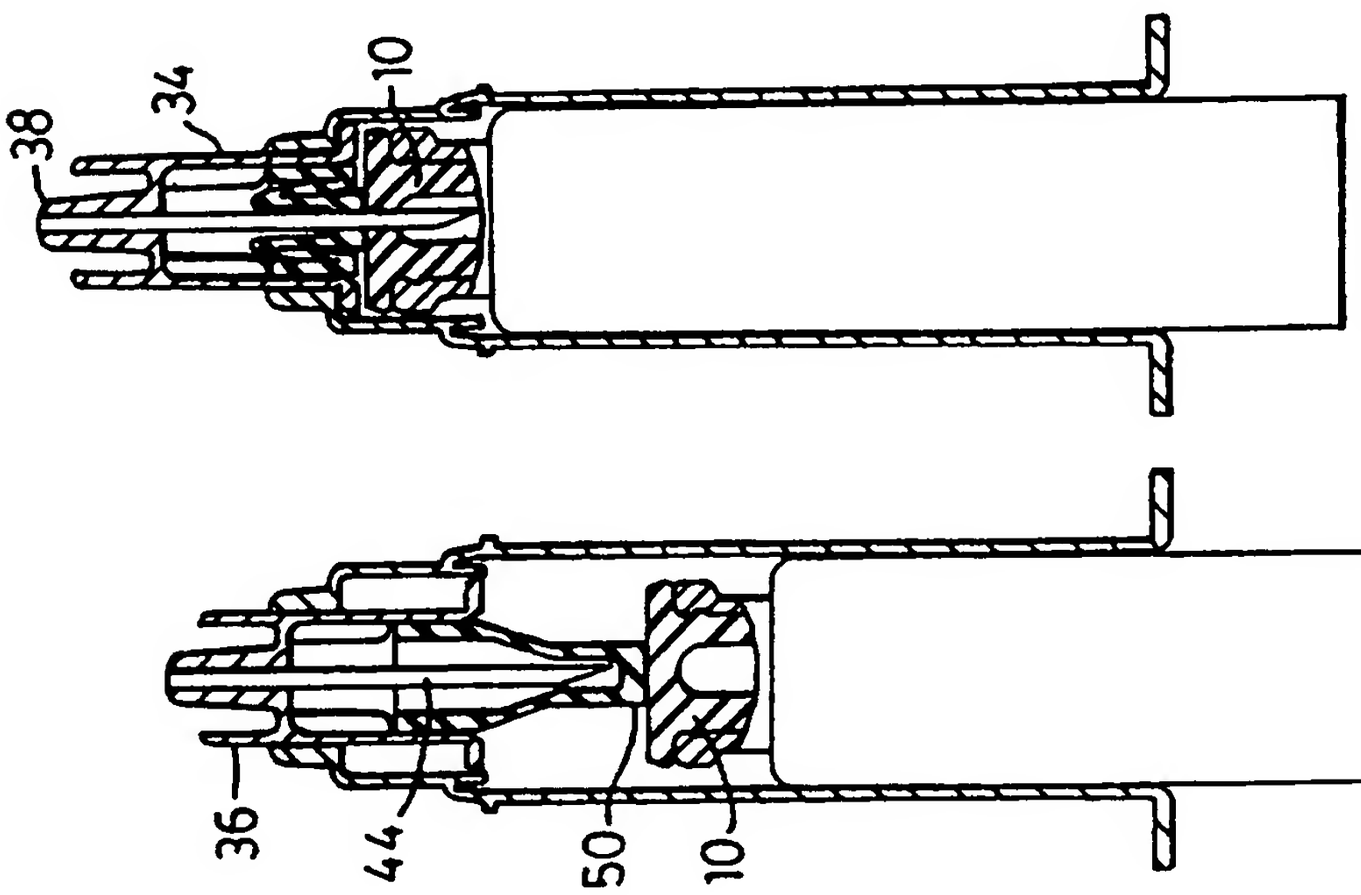

FIG.5

FIG.4

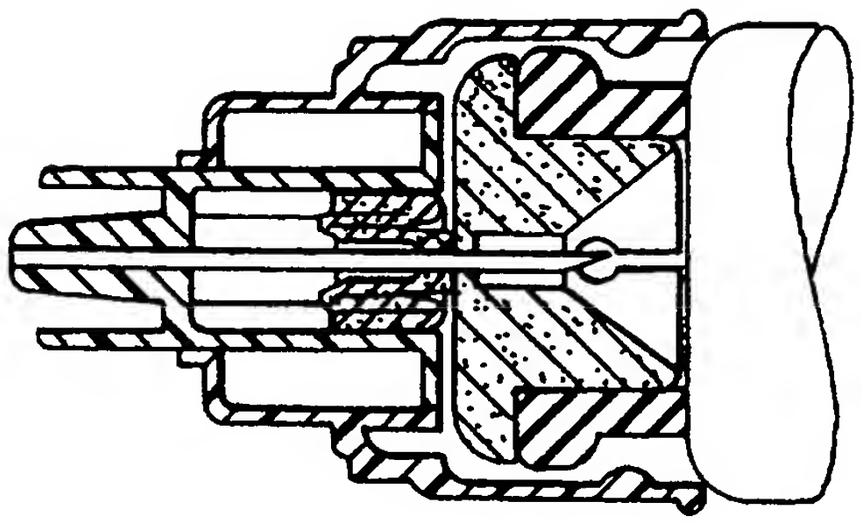

FIG.12

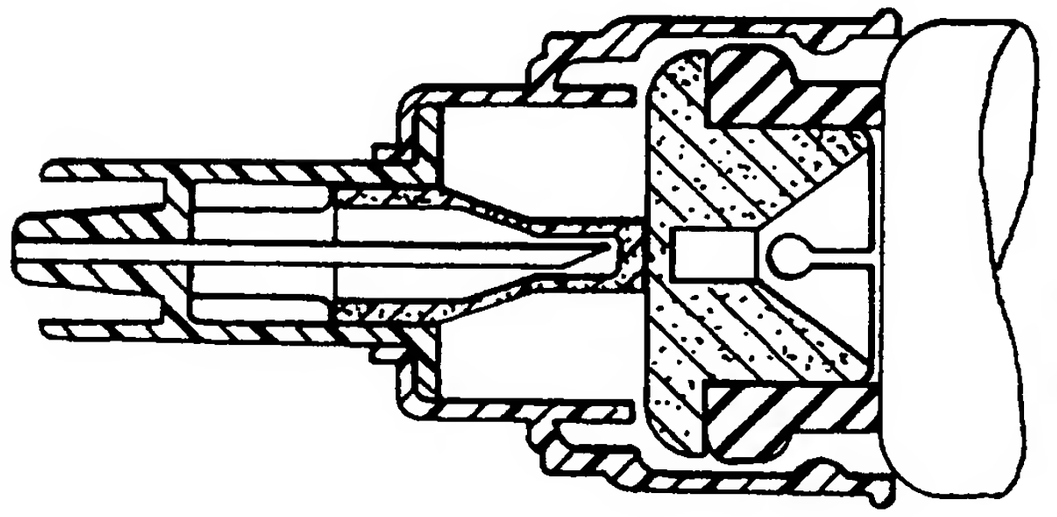

FIG.11

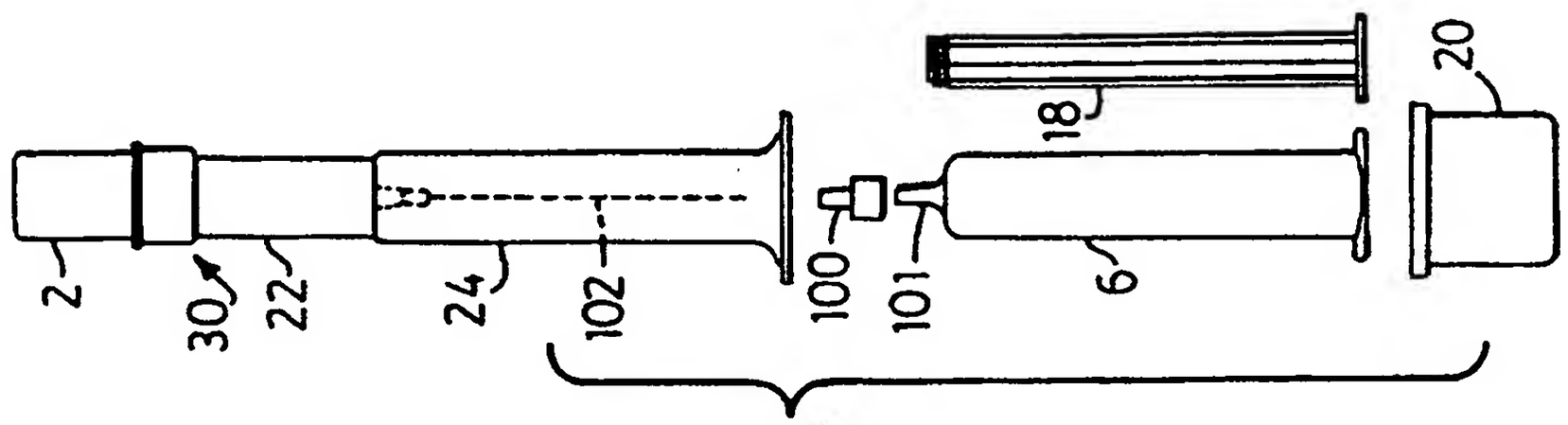

FIG.10

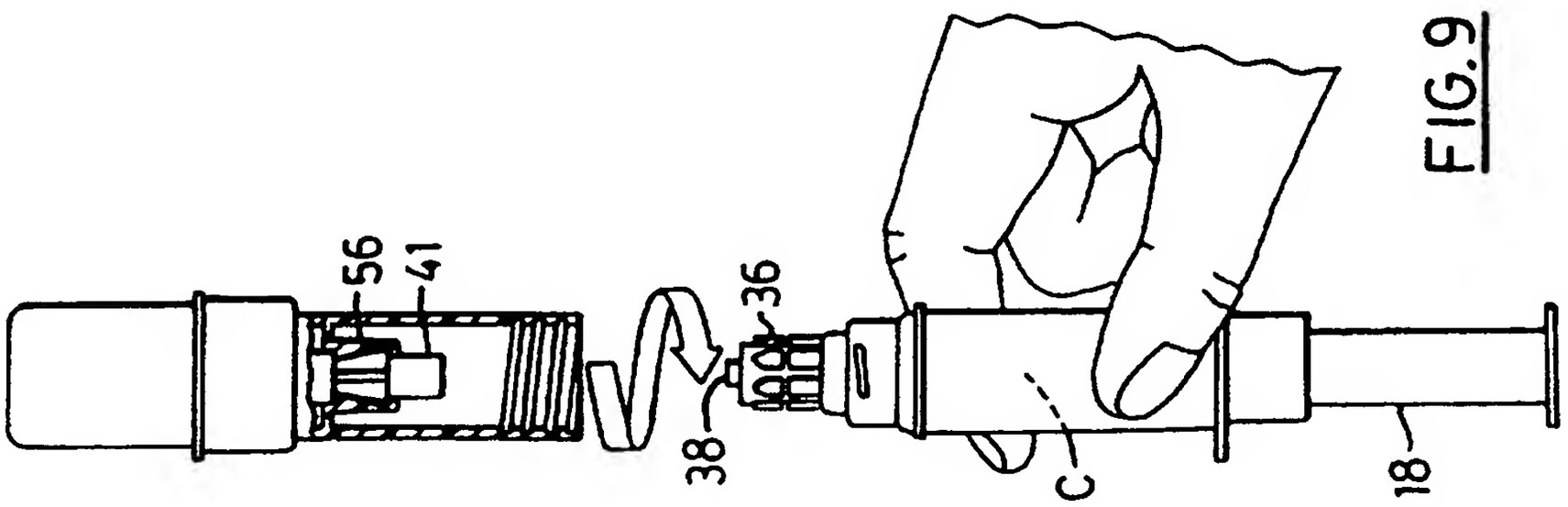

FIG.9

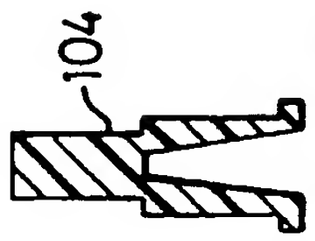

FIG.13

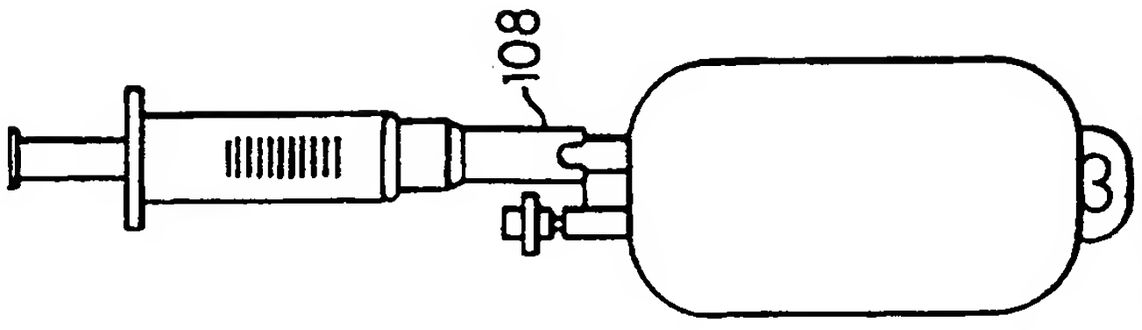

FIG.16

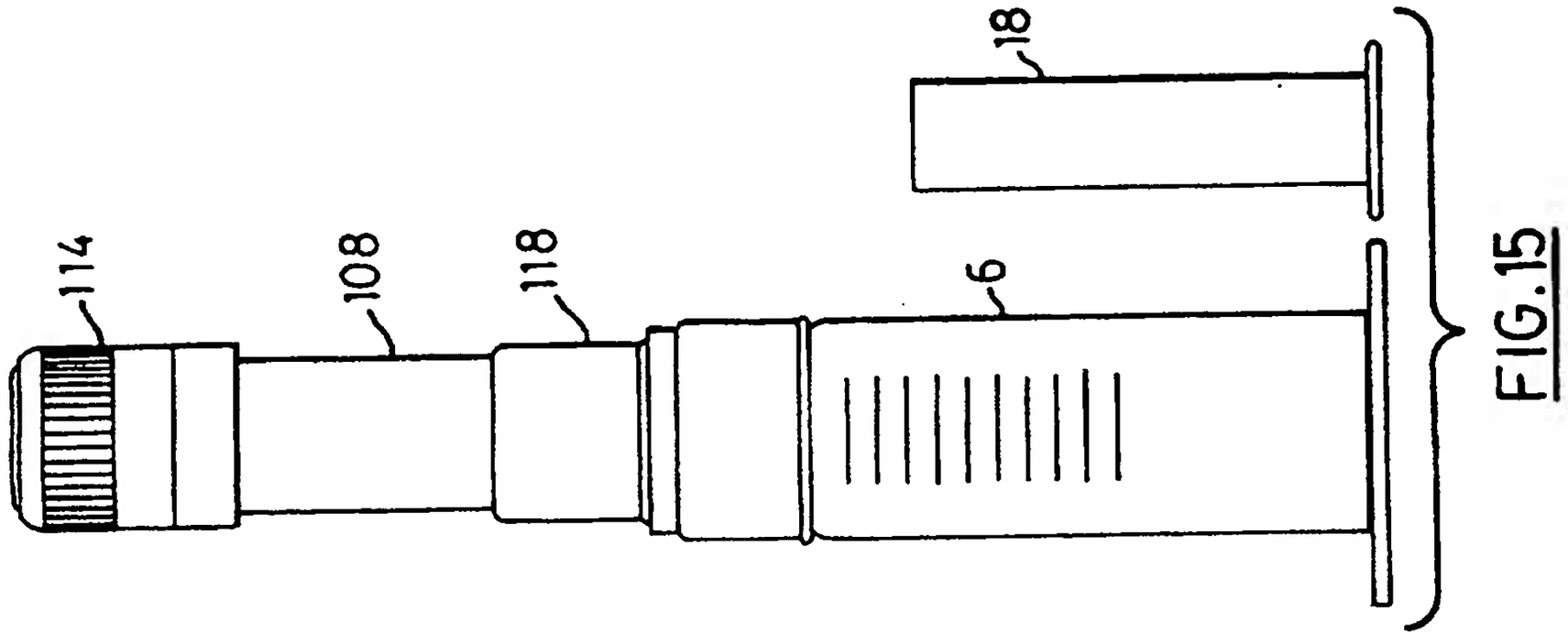

FIG.15

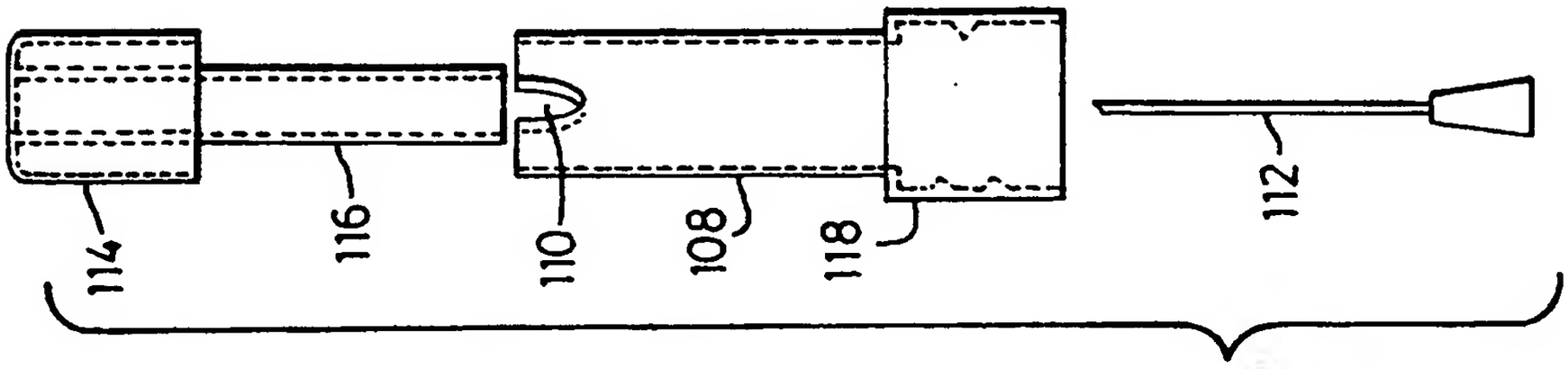

FIG.14

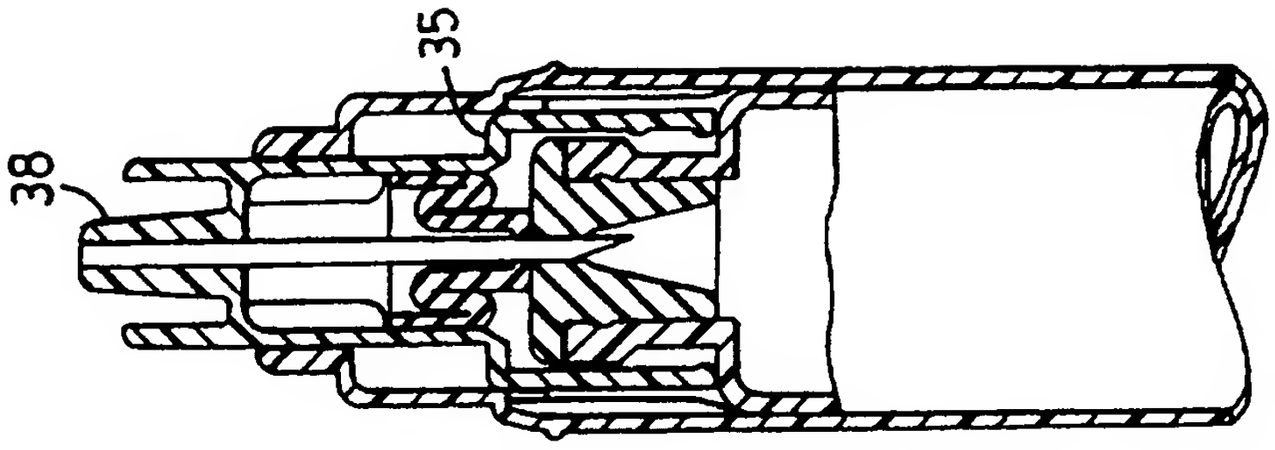

FIG.20

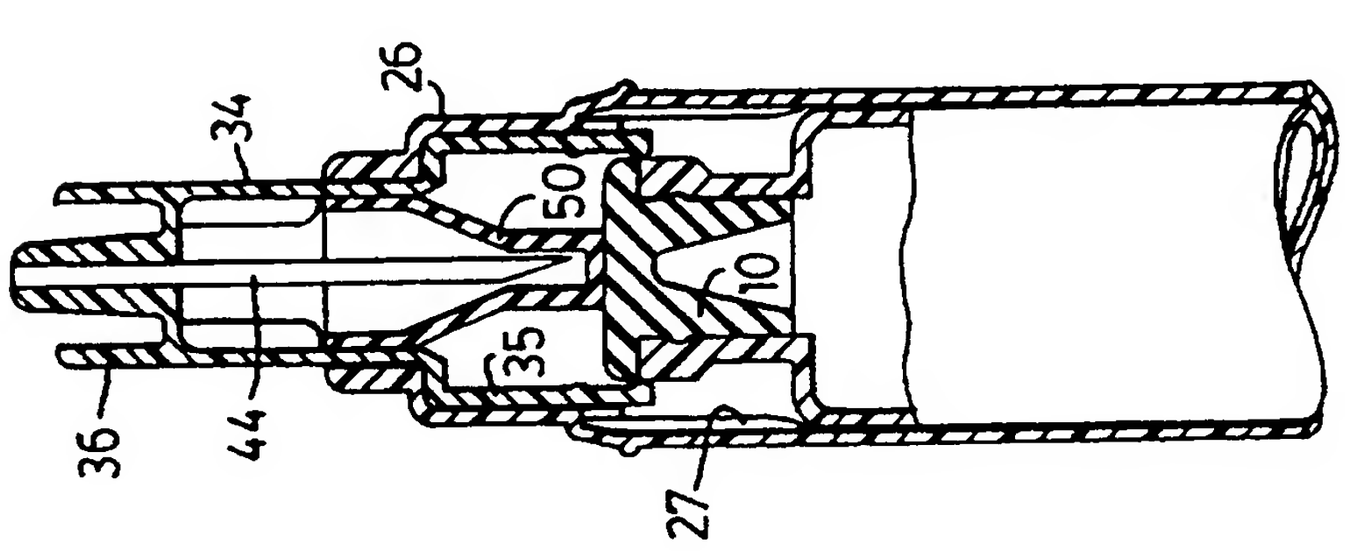

FIG.19

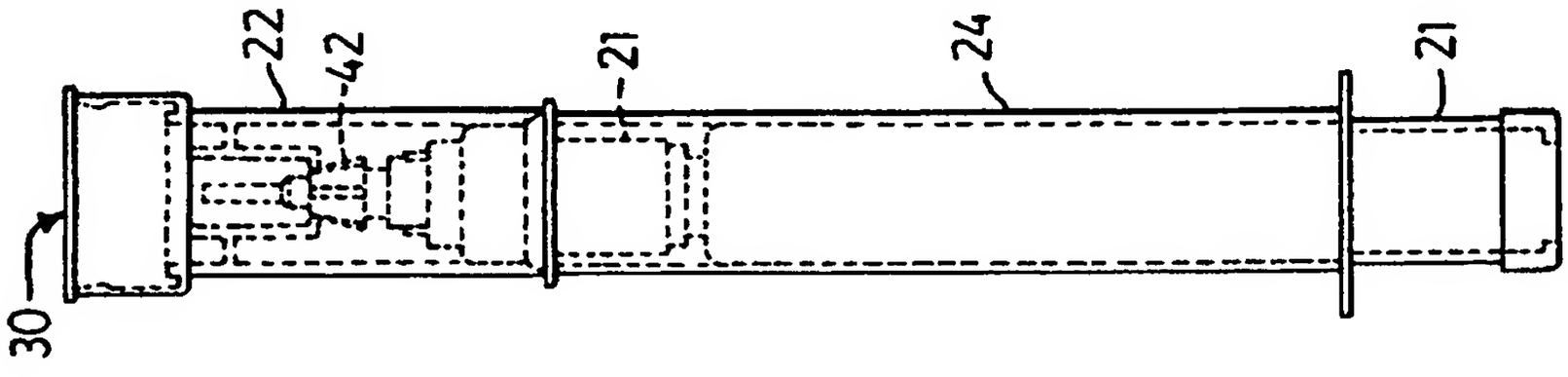

FIG.18

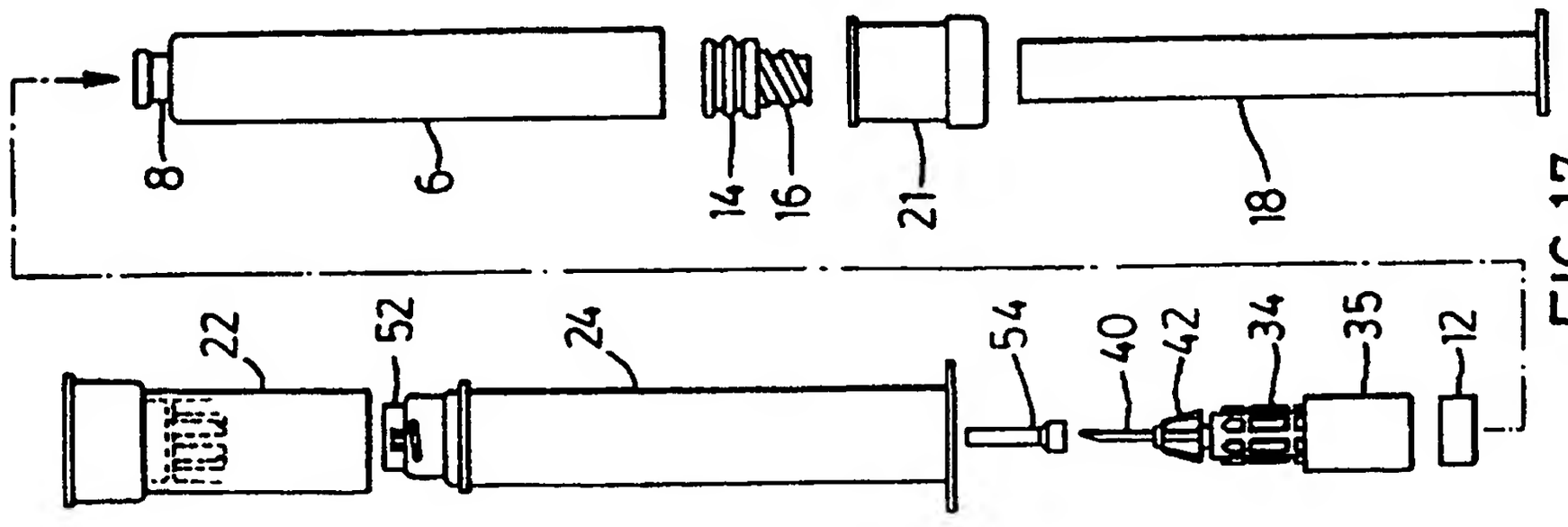

FIG.17

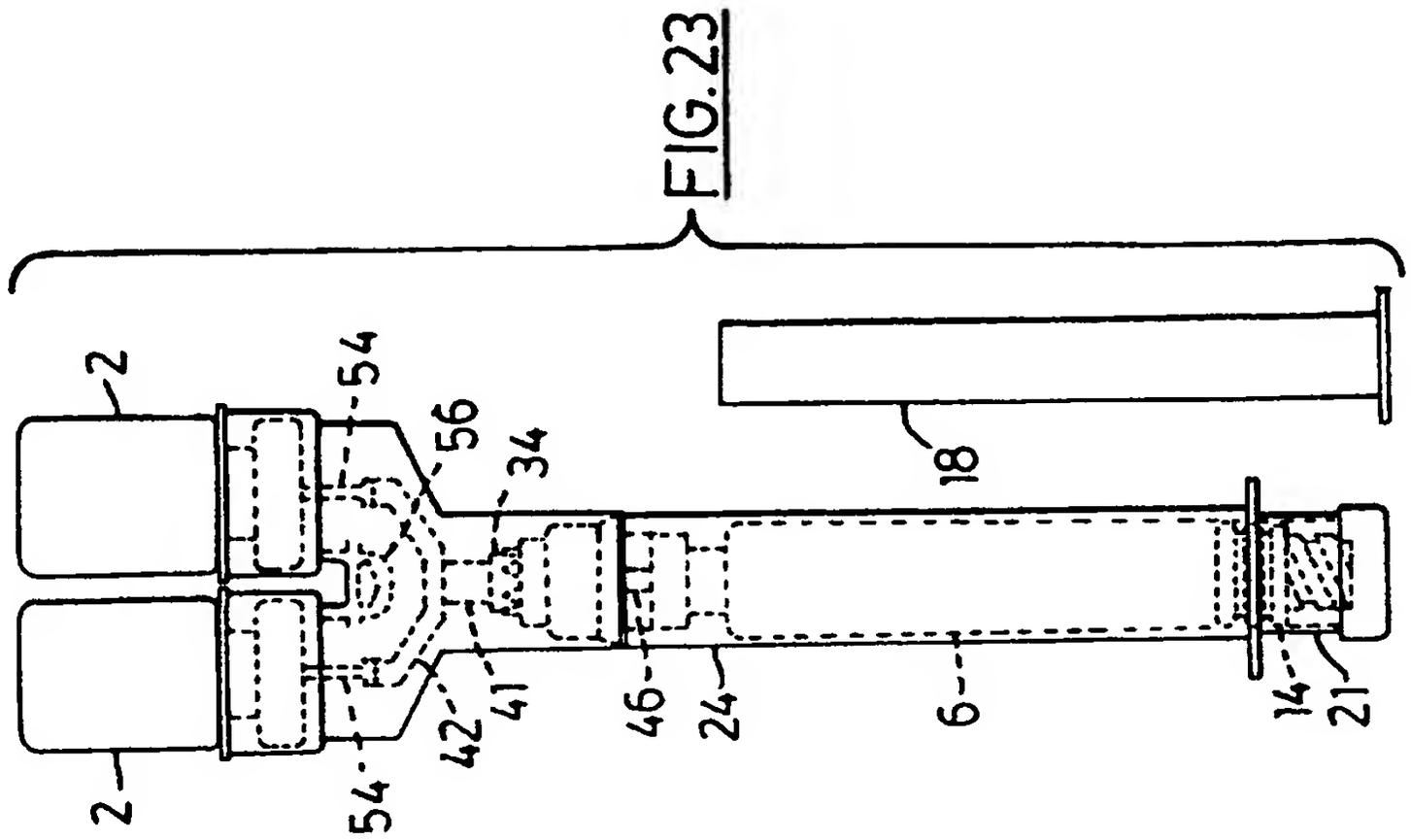

FIG.23

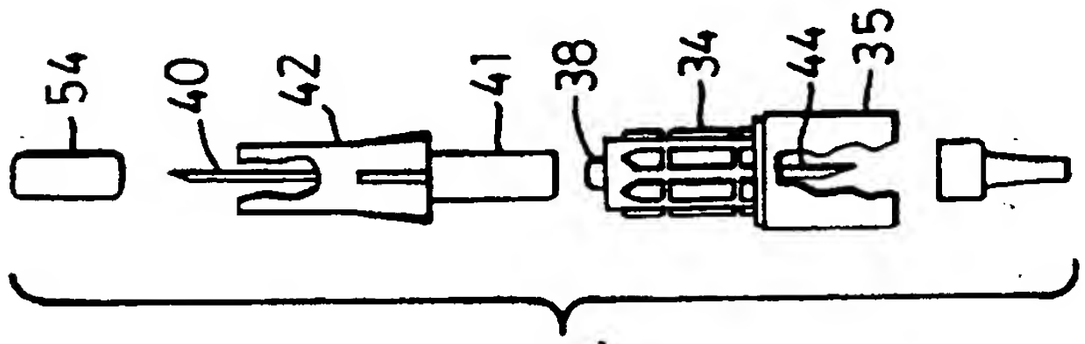

FIG.22

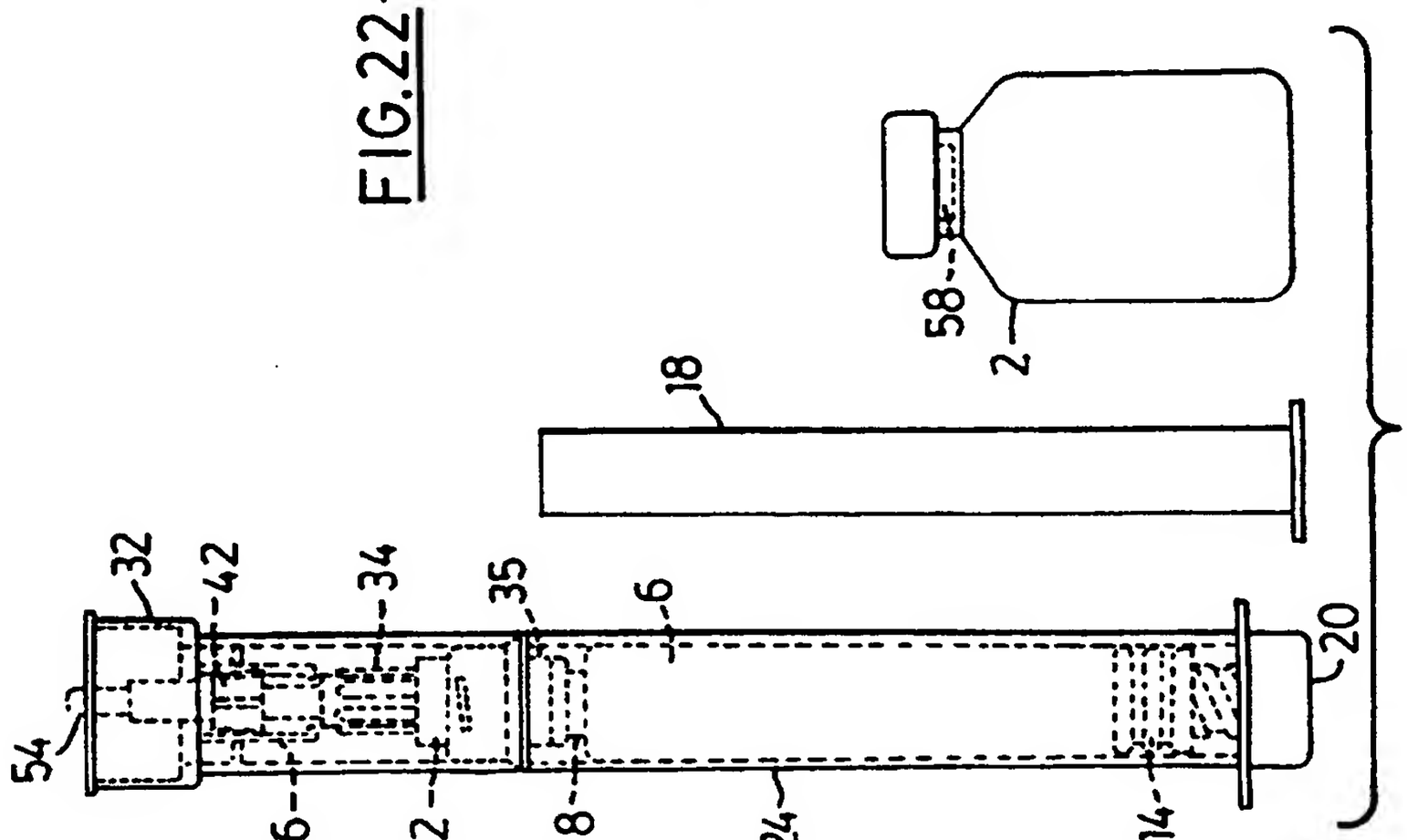

FIG.21

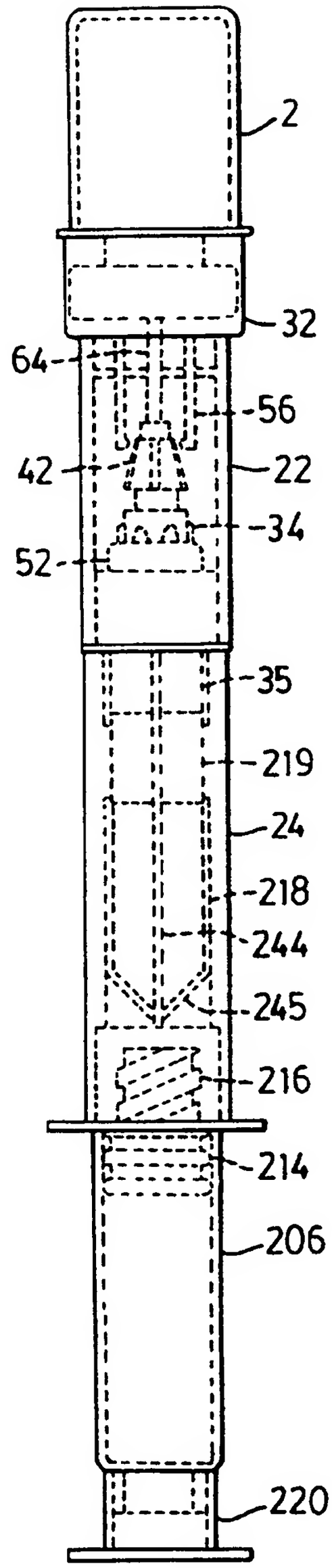

FIG.24

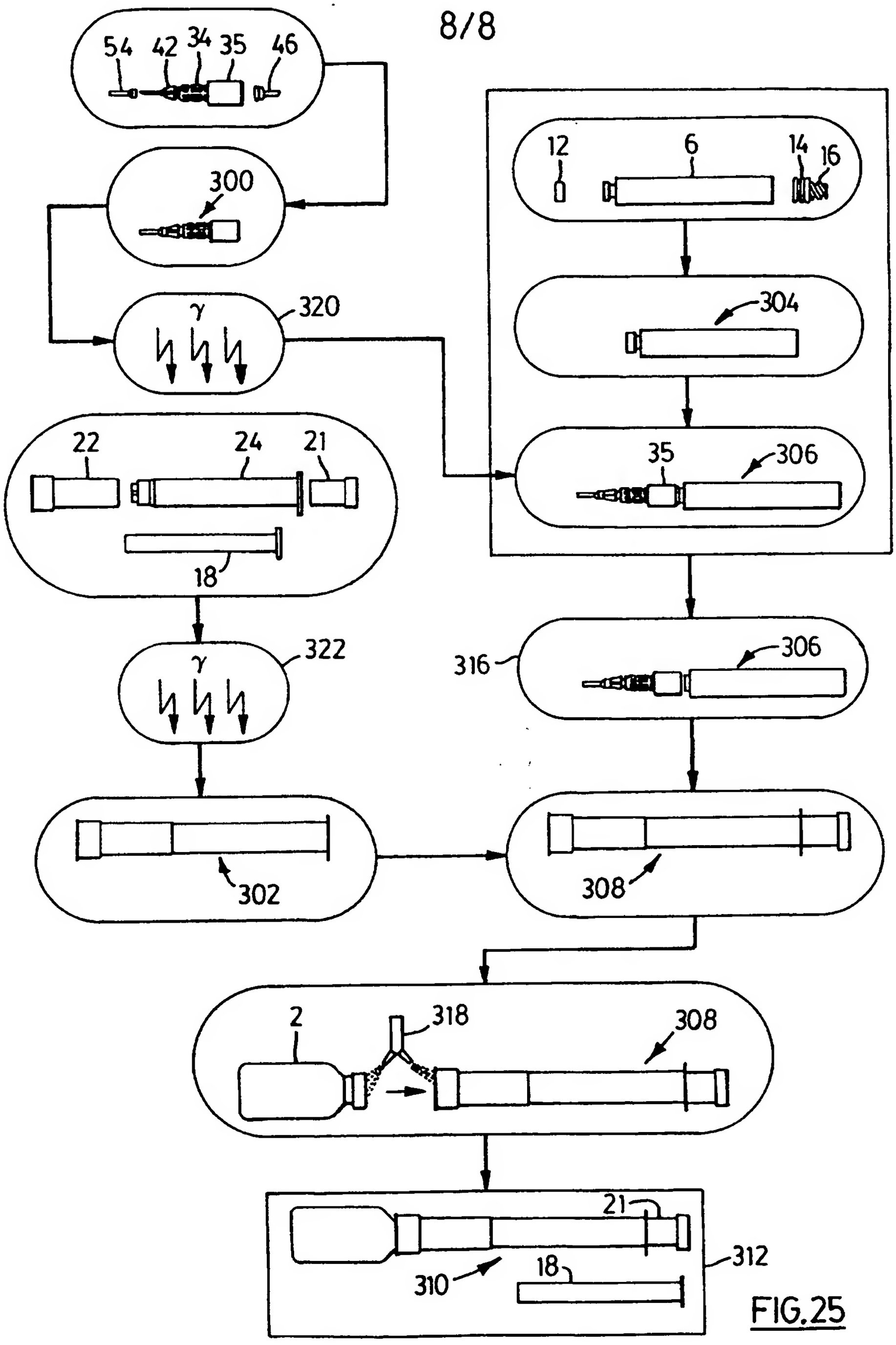
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FIG.25

INTERNATIONAL SEARCH REPORT

Int' tional Application No
PCT/CA 97/00017

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	DE 19 13 926 A (FARBWERKE HOECHST AG) 24 September 1970 see page 3, line 8 - page 5, line 8 see figures 2-4	1,3,7
Y		2,4-6, 11-13,24
A		10,20, 22,23

Y	EP 0 335 378 A (FUJISAWA PHARMACEUTICAL CO.) 4 October 1989 see column 4, line 8 - column 6, line 53 see figures 1,2,12-14,22	2,11-13
A		9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1997	12.05.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	**Authorized officer** Schönleben, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In· tional Application No
PCT/CA 97/00017

C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 11897 A (ABBOTT LABORATORIES) 23 July 1992 see page 7, line 24 - page 9, line 21 see figures 1-7	4-6,24
A	& US 5 171 214 A cited in the application	8,19
X	WO 90 03536 A (BAXTER INTERNATIONAL) 5 April 1990 see page 9, line 17 - page 14, line 27 see figures 1-5	1
A		9

2

INTERNATIONAL SEARCH REPORT

...ternational applicauon No.
PCT/CA 97/00017

Box I ()bservations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

No.1: Claims 1-10,22,23,24
Activation assembly comprising a hub.

No.2: Claims 11-21,23
Activation assembly comprising a hub and an overcap.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/CA 97/00017

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PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 5/315

A1

(11) International Publication Number: WO 98/13088

(43) International Publication Date: 2 April 1998 (02.04.98)

(21) International Application Number: PCT/US97/17194

(22) International Filing Date: 25 September 1997 (25.09.97)

(30) Priority Data:
722,603 27 September 1996 (27.09.96) US

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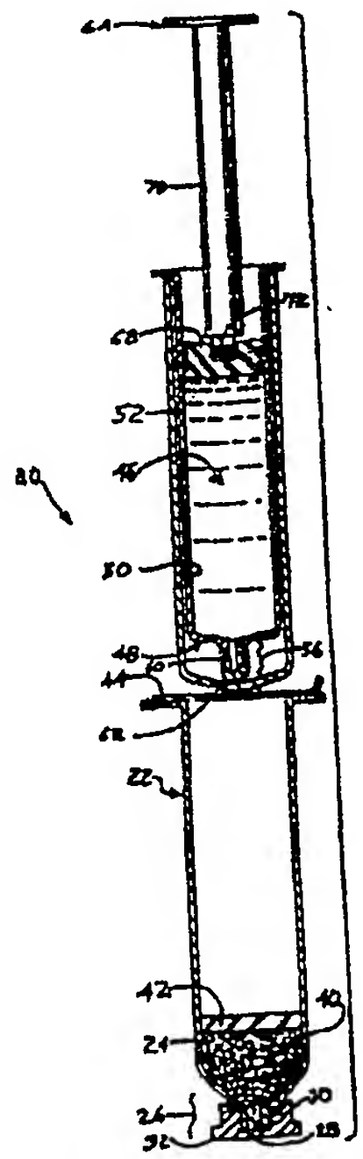
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYRINGE SYSTEM ACCOMMODATING SEPARATE PREFILLED BARRELS FOR TWO CONSTITUENTS

(57) Abstract

A prefilled, two–constituent system is provided with first and second containers or barrels. The first barrel includes a first chamber having a dispensing end or delivery end. The delivery end defines a dispensing passage or delivery passage communicating through the delivery end to accommodate the dispensing of fluid from the first chamber. A movable seal or reciprocable stopper is slidably disposed in the first chamber, and a first constituent is provided in the first chamber between the delivery end and the stopper. A second container or barrel is sized to be disposed in the first barrel and has a discharge end defining a discharge passage communicating through the discharge end to accommodate the discharge of fluid from the second barrel. A plunger is slidably disposed within the second barrel. A liquid second constituent is provided in the second barrel between the discharge end and the plunger. The first barrel stopper and the second barrel discharge end are engageable directly or indirectly to cooperatively define a coupling accommodating the flow of the liquid second constituent from the second barrel into the first chamber of the first barrel as the second barrel moves outwardly relative to the first chamber.



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SYRINGE SYSTEM ACCOMMODATING SEPARATE PREFILLED BARRELS FOR TWO CONSTITUENTS

This is a continuation-in-part of U.S. Patent Application Serial No. 08/408,463 filed March 22, 1995.

TECHNICAL FIELD

This invention relates to a syringe system for packaging, mixing and delivering two constituents or components that are stored separately in isolation from each other but which must be combined or mixed together prior to delivery. The invention is particularly suitable for use with a medicament, such as a drug in powder form, which must be dissolved and diluted in a liquid prior to delivery.

BACKGROUND OF THE INVENTION AND TECHNICAL PROBLEMS POSED BY THE PRIOR ART

In some medical applications, as well as in some industrial or other applications, it is necessary, or at least preferable, to maintain two components or constituents in isolation prior to combining the two components for subsequent delivery as a solution, mixture, or other combination.

For example, some pharmaceutical preparations, such as injectable solutions or suspensions of a drug, are not sufficiently stable to accommodate prolonged storage prior to use. However, the components of the solution or suspension may have adequate stability if the components are stored separately prior to being combined.

It would be desirable to provide an improved syringe system that will accommodate the packaging of two such components in isolation from each other, but which can be subsequently operated to combine or mix the components for delivery. In particular, it would be advantageous to provide such an improved syringe system

with the capability, where necessary, for employing component prefilled barrels that can be manufactured and/or stored separately as well as together.

It would be especially advantageous if such an improved system could be employed with two liquid components as well as with at least one solid component.

It would be desirable with such a system to positively seal both components from the ambient atmosphere as well as from each other.

It would also be beneficial if such an improved system could be provided in a self-contained form that is compact, portable, simple to manipulate, and readily adaptable to different proportions and dosages of the components.

Additionally, it would be desirable if such an improved system could readily accommodate the storage, mixing and administration of a variety of drugs which require reconstitution and/or dilution including, among other types, a medicament in powder form requiring mixing with a diluent, a medicament in liquid form requiring mixing with a diluent, and a lyophilized compound requiring mixing with a diluent.

The present invention provides an improved packaging, mixing and delivery system which can accommodate embodiments having the above-discussed benefits and features.

SUMMARY OF THE INVENTION

The present invention provides a syringe system for storing two components or constituents in isolation from each other. The system can be subsequently operated for combining or mixing the two constituents and for then delivering the combination.

The syringe system includes first and second prefilled containers which each includes first and second

prefilled syringe barrels, respectively. The first barrel includes an open end and an opposite substantially closed delivery end. The delivery end defines a delivery passage or dispensing passage to accommodate the delivery or dispensing of fluid from the first barrel. Preferably, a first removable closure is provided to occlude the delivery passage. A reciprocable stopper or moveable seal is slidably disposed in the first barrel to define a first chamber. The first chamber is preferably prefilled with a first constituent between the reciprocable stopper and the delivery end.

The second barrel is sized to be disposed in the first barrel and has an open end and an opposite substantially closed discharge end having a discharge passage to accommodate the discharge of fluid from the second barrel. Preferably, a second removable closure is provided to occlude the discharge passage. A slidable plunger is sealingly disposed within the second barrel to define a second chamber. The second barrel is preferably prefilled with a liquid second constituent in the second chamber between the discharge end and the slidable plunger.

In order to combine the two constituents, the second closure, if any, is first removed from the second barrel discharge end. The first barrel reciprocable stopper and the second barrel discharge end are engageable to cooperatively define a coupling or fluid transfer connector means for accommodating the flow of the liquid second constituent from the second chamber into the first chamber. This can include (a) connecting means for connecting the second barrel with the reciprocable stopper in the first barrel, and (b) fluid communicating means for establishing fluid communication between the first and second chambers. As the second barrel discharge end and

plunger are moved closer together, the liquid constituent is moved (i.e., pushed) from the second chamber into the first chamber where the liquid second constituent mixes with the first constituent. The assembly may be shaken to promote mixing.

Subsequently, the first closure can be removed from the first barrel. Then the second barrel, which is engaged with the reciprocable stopper, can be pushed inwardly. This movement carries both the second barrel and coupled reciprocable stopper inwardly into the first chamber. This coupled movement dispenses the mixed contents of the first chamber through the delivery passage.

Numerous other advantages and features of the present invention will become readily apparent from the following detailed description of the invention, from the claims, and from the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the accompanying drawings that form part of the specification, and in which like numerals are employed to designate like parts throughout the same,

FIG. 1 is a partial cross-sectional view of a first embodiment of the syringe system of the present invention showing the first and second containers before the container barrels are coupled together;

FIG. 2 is a greatly enlarged, fragmentary, cross-sectional view of the discharge end of the second barrel;

FIG. 3 is a view of the components of FIG. 1 in a coupled condition with the reciprocable stopper in the first barrel penetrated by the piercing needle of the second barrel just prior to the plunger of the second barrel being moved toward the discharge end;

FIG. 4 is a view similar to FIG. 3, but FIG. 4 shows the liquid contents of the second barrel completely discharged into the first barrel;

FIG. 5 is a greatly enlarged, fragmentary, cross-sectional view of the delivery end of the first barrel shown with the first closure removed and replaced with a needle;

FIG. 6 is a cross-sectional view of a second embodiment of the present invention showing the separate first and second barrels of the containers prior to being coupled together;

FIG. 7 is a greatly enlarged, fragmentary, cross-sectional view of the conduit assembly and reciprocable stopper in the first barrel of the second embodiment;

FIG. 8 is a perspective view of the valve member employed in the reciprocable stopper of the second embodiment;

FIG. 9 is a top plan view of the valve member shown in FIG. 8;

FIG. 10 is a view similar to FIG. 7, but FIG. 10 shows a third embodiment of the present invention having a modified reciprocable stopper;

FIG. 10A is a fragmentary, bottom plan view taken along the plane 10A-10A in FIG. 10;

FIG. 11 is a cross-sectional view of a fourth embodiment of the present invention showing the separate first and second barrels of the containers prior to being coupled together;

FIG. 12 is a greatly enlarged, fragmentary, cross-sectional view of a portion of the assembled components of the fourth embodiment showing the second barrel being operated to open the mixing valve of the first barrel;

FIG. 13 is a cross-sectional view of a fifth embodiment of the present invention showing the separate first and second barrels of the containers prior to being coupled;

FIG. 14 is a greatly enlarged, fragmentary, cross-sectional view of a portion of the assembled components of the fifth embodiment showing the second barrel being operated to open the mixing valve of the first barrel;

FIG. 15 is a cross-sectional view taken generally along the plane 15-15 in FIG. 14;

FIG. 16 is a cross-sectional view taken generally along the plane 16-16 in FIG. 15; and

FIG. 17 is a fragmentary, cross-sectional view of a portion of the assembled components of a sixth embodiment of the present invention showing the second barrel being operated to open the mixing valve in the first barrel.

DESCRIPTION OF THE PREFERRED EMBODIMENT

While this invention is susceptible of embodiment in many different forms, this specification and the accompanying drawings disclose only some specific forms as examples of the invention. The invention is not intended to be limited to the embodiments so described, however. The scope of the invention is pointed out in the appended claims.

Figures illustrating the apparatus show some mechanical elements that are known and that will be recognized by one skilled in the art. The detailed descriptions of such elements are not necessary to an understanding of the invention, and accordingly, are herein presented only to the degree necessary to

facilitate an understanding of the novel features of the present invention.

A first embodiment of the prefilled syringe system of the present invention is illustrated in FIGS. 1-5 and is designated generally therein by the reference number 20. The system may be generally characterized as including two "containers" for separately storing two constituents or components in isolation from each other, but which can be subsequently operated to combine or mix the components for delivery. The first container includes a first barrel 22 having an open end 24 and an opposite, substantially closed, dispensing end or delivery end 26 defining a delivery passage or dispensing passage 28. The first barrel 22 is preferably fabricated from a synthetic polymer, such as a thermoplastic material, but the barrel may be made of other suitable material such as glass.

A first constituent or component 40 is provided in the first barrel 22. The constituent 40, in the preferred embodiment contemplated for use in medical applications, can be a drug or other medicament in granular form, powder form, or other particulate form. The first constituent may also be a liquid. It is contemplated that the constituent 40 in the first barrel 22 would typically be a drug which, if in solid form, requires reconstitution, or if in liquid form, requires dilution. Thus, the system of the present invention will be useful in the containment of hazardous drugs such as are used in oncological applications or in biotechnology delivery applications.

Preferably, the delivery end 26 defines an exterior thread form 30 for receiving a threaded cap or first removable closure 32 and for subsequently receiving, upon removal of the closure 32, a suitable dispensing component, such as a hollow needle 34 described

hereinafter in detail with reference to FIG. 5. Any other suitable conventional or special capping system may be employed.

A reciprocable stopper 42 is slidably disposed in the first chamber 24 above the first constituent 40. Preferably, the reciprocable stopper 42 is fabricated from a resilient, elastomeric material. In the preferred form, the reciprocable stopper 42 has an uncompressed diameter somewhat larger than the diameter of the chamber 24. A friction-fit engagement is established between the stopper 42 and the chamber 24 that is sufficient to hold the stopper 42 in place on top of the constituent 40 during normal packaging, shipping and handling. However, the force of engagement is sufficiently low to permit sliding of the stopper 42 along the chamber 24 when the stopper 42 is subjected to a sufficiently high axial force as described in detail hereinafter.

The reciprocable stopper 42 may be alternatively described as a moveable seal, slidable seal, piston, or grommet. All of these terms may be regarded as interchangeable herein. The term "moveable seal" has been used in the above-identified parent patent application Serial No. 08/408,463. However, the term "reciprocable stopper" is generally used herein to define the same or analogous components.

As illustrated in Fig. 1, it is also preferred to provide an outer cover 44 over the upper, open end of the first container barrel 22. This prevents ingress of contaminants. The cover 44 may be an adhesive backed, flexible web that can be readily pulled off just prior to use of the system.

The first barrel 22 may be regarded as a first container together with the closure 32, stopper 42, and cover 44 for storing the first component 40 and

subsequently mixing the first component 40 with another component as explained in detail hereinafter.

A second constituent or component 46, in the form of a liquid, is sealed within a second barrel 48. The liquid constituent 46 would typically be a diluent for diluting and/or reconstituting the first constituent 40. The second barrel 48 may be formed from the same synthetic polymer materials as used for the first container 22.

The second barrel 48 preferably includes a generally cylindrical wall portion 50 that is sized to be disposed in the first container 22 (FIGS. 3 and 4). Initially, in the pre-assembled condition, the second barrel 48 is preferably encased in a protective sleeve 52 which must be removed prior to use.

The second barrel 48 also includes a plunger assembly or plunger assembly or plunger 64 which is slidably disposed within the cylindrical barrel 50. The plunger 64 includes a plunger shank or stem 70 with a thumb push flange at one end and a piston 68 at the other end slidably received within the barrel cylindrical wall portion 50.

The piston 68 is preferably elastomeric and is initially located at the upper end of the second barrel 48 in contact with the liquid second constituent 46 as illustrated in FIG. 1. For packaging convenience, the plunger shank 70 may be provided with a threaded end or snap-fit end 72 for engaging a mating thread form or snap-fit form in the top of the piston 68. Such a structure permits packaging of the system components with the plunger shank 70 not initially connected or assembled with the piston 68. When it is subsequently desired to use the system, the user can thread or snap-fit the shank 70 into the piston 68.

The second barrel 48 has a discharge end 56 defining a discharge passage communicating through the discharge end to accommodate the discharge of fluid from the barrel 48. In the first embodiment illustrated in FIGS. 1-5, the second barrel discharge passage is defined by the hollow interior of a piercing needle 60 which is mounted in the discharge end of the second barrel 48.

Preferably, the second barrel 48 is initially provided to the user with a second cap or removable closure 62 mounted to the second barrel discharge end 56 over the piercing needle 60 as shown in FIG. 2. The second closure 62 may be held on the discharge end of the second container by means of a snap-fit (or by other means, e.g.; a threaded engagement (not illustrated).

The second barrel 48 may be regarded as a second container together with the closure 62 and plunger 64 for storing and subsequently functioning as a syringe to discharge the liquid second constituent 46 into the first container barrel 22 as will be explained in detail hereinafter.

The operation of the packaging syringe system 20 will next be described with reference to the sequential operational steps illustrated in FIGS. 3-5. The first stage of the operation is illustrated in FIG. 2.

Just prior to use, the second closure 62 is removed to expose the piercing needle 60. Preferably, before the second closure 62 is removed, the second barrel 48 is inverted (so that the piercing needle 60 is pointing generally upwardly). This will ensure that the liquid constituent 46 cannot drip out. However, even if the second barrel 48 is not inverted, the liquid constituent 46 will not drip out. This is because the second barrel 48 has no vent system. A vent system would admit ambient air into the second barrel 48 so as to permit the liquid

constituent to flow out through the needle 60 solely under the influence of gravity. Without such venting, the liquid constituent 46 remains in the second barrel 48 and is not able to flow out through the piercing needle 60.

With the second barrel 48 preferably inverted to point the piercing needle 60 upwardly, the first barrel 22 is inverted and aligned with the second barrel 48. Then relative movement is effected so as to locate the distal end of the second barrel 48 in the first barrel 22. As illustrated in FIG. 3, the second barrel 48 is inserted into the first barrel 22 until the piercing needle 60 engages, and penetrates completely through, the reciprocable stopper 42 of the first barrel 22.

Before and during the step of inserting the second barrel 48 inside the first barrel 22, the moveable plunger 64 is not moved relative to the second container 48. The plunger 64 remains in the initial, outermost orientation. After the two barrels are telescopically disposed with the piercing needle 60 fully penetrating the stopper 42 in the first barrel 22, the plunger 64 is pushed inwardly within the second barrel 48 (i.e., toward the discharge passage in the needle 60 of the second barrel 48). The plunger movement causes the liquid second constituent 46 to flow out through the hollow piercing needle 60 to mix with the first constituent 40 within the first chamber 24. The hydraulic pressure within the first chamber 24 acts on the stopper 42 and the abutting distal end of the second barrel 48. The increasing pressure moves (i.e., pushes) the reciprocable stopper 42 and the second barrel 48 outwardly relative to the first barrel 22. It will be appreciated that the ambient atmospheric pressure bears on the outside surface of the plunger piston 68, and this additional pressure is effective in

aiding the discharge of the liquid second constituent 46 into the first chamber 24.

When the piston 68 is seated at the bottom, discharge end of the second barrel 48, the top, open end of the second barrel 48 is adjacent to the thumb push flange at the top of the plunger 64 (as shown in FIG. 4). Substantially all of the liquid second constituent has been discharged through the hollow piercing needle 60 into the first chamber 24 of the first barrel 22 where it forms a solution with, mixes with, or is otherwise combined with the first constituent 40. The assembly can be shaken to ensure good mixing.

After the constituents are sufficiently mixed, the first closure 32 is removed from the first barrel 22, and the delivery end 26 can be connected to a receiving component or discharge component, such as a flexible container or tubing set (not illustrated). Optionally, a hollow needle 34 is mounted at the distal end of the first barrel delivery end 26. The needle 34 may be of a conventional, single-ended type with a straight, hollow, stainless steel shaft, typically 20 gauge in size. The needle 34 may be provided with a swaged or molded hub 74 (FIG. 5) for engagement with the bottom, distal end of the delivery end 26 of the first barrel 22.

When properly mounted on the first barrel 22, the needle 34 is in alignment with the delivery passage 28, and fluid communication is established between the delivery passage 28 and the needle 34. After the needle 34 is properly mounted on the first barrel 22, (or after the first barrel 22 is otherwise properly connected to some suitable receiving component), the plunger 64 and second barrel 48 can be moved forward by applying an axial force. This causes the combined constituents in the first

chamber 24 to be dispensed or expelled from the chamber 24 through the needle 34.

It will be appreciated that the first barrel stopper 42 has a central portion which is fully penetratable by the needle 60. That stopper central portion and the second barrel piercing needle 60 cooperatively define a fluid transfer connector means or coupling means incorporating (a) fluid communicating means and (b) connecting means. The fluid communicating means includes the flow passage through the needle 60 which is operative to accommodate the flow of the liquid second constituent from the second barrel 48 into the first chamber 24 of the first barrel 22. The connecting means includes the sealing engagement between the exterior of the needle 60 and the stopper 42 which accommodates the movement of the stopper 42 together with the second barrel 48--first outwardly as the liquid second constituent 46 is moved (i.e., forced or pushed) into the first chamber 24, and subsequently inwardly outwardly into the first chamber 24 to dispense the combined constituents.

An alternate second embodiment of the syringe system of the present invention is illustrated in FIGS. 6-9. Elements in the alternate embodiment which are the same as, or which function in an analogous manner to, elements of the first embodiment illustrated in FIGS. 1-5 are designated with three digit reference numbers wherein the last two digits are the same as the two digits of the reference number of the corresponding element in the first embodiment.

With reference to FIG. 6, the second embodiment of the syringe system includes a first barrel 122 and a second barrel 148. The first barrel 122 has an open upper end which is initially sealed with a removable cover 144. The first barrel 122 contains a first component or

constituent 140. The first constituent 140 is deposited in the bottom of the first barrel 122 which defines a dispensing end or delivery end 126 having a dispensing passage or delivery passage 128 communicating through the dispensing end or delivery end 126 to accommodate the dispensing of fluid from the first chamber 124.

The closed delivery end 126 preferably includes a concentrically extending collar with an interior threaded form for receiving a first removable closure 132 as shown in FIG. 6. Upon removal of the closure 132, the delivery end 126 can be threadably mated with a suitable receiving component, such as a stopcock or an IV administration set (not illustrated).

A reciprocable stopper 142 is slidably disposed in the first barrel 122 and, together with the first barrel 122, defines a first chamber 124 which is initially filled with the first constituent 140. The stopper 142 is retained with sufficient frictional engagement to prevent its movement within the first barrel 122 during normal storage, transport, and handling.

The reciprocable stopper 142 may be alternatively described as a moveable seal, slidable seal, piston, or grommet. All of these terms may be regarded as interchangeable herein. The term "moveable seal" has been used in the above-identified parent patent application Serial No. 08/408,463. However, the term "reciprocable stopper" is generally used herein to define the same or analogous components.

Preferably, the reciprocable stopper 142 is fabricated from a resilient elastomeric material. In the preferred form, the reciprocable stopper 142 has an uncompressed diameter somewhat larger than the diameter of the first barrel 122 for a friction-fit slidable engagement with the first barrel 122. The reciprocable

stopper 142 is retained with sufficient frictional engagement to prevent its movement with the first barrel 122 during normal storage, transport, and handling.

As can be seen in FIG. 7, a novel conduit and valve assembly 176 is mounted in the reciprocable stopper 142. The conduit and valve assembly 176 includes a generally elongate conduit 177 (which may be in the form of a luer socket) extending through the stopper 142 and defining an internal flow passage 178 having an inlet 177A and an outlet 177B.

The conduit and valve assembly 176 includes a laterally projecting boss 180 defining a receiving cavity 181 for receiving a ribbed anchor portion 184 of a valve member insert 185. The valve member insert 185 includes a transversely oriented, resilient, spring member 186 extending from the lower end of the anchor portion 184. A frusto-conical, flapper valve member 187 projects upwardly from the spring member 186. The exterior surface of the valve member 187 is adapted to seal against the conduit outlet 177B. The spring member 186 normally biases the valve member 187 in tight sealing engagement against the conduit outlet end 177B as illustrated in FIG. 7. This defines a one-way flow valve.

The inlet end of the conduit and valve assembly 176 includes a standard female luer socket which defines the inlet 177A and from which extends a connector flange 179, such as is employed in conventional connection systems marketed under the trademark LUER-LOK. This accommodates connection of the conduit and valve assembly 176 to the second barrel 148 as described in detail hereinafter. Other suitable conventional or special connecting systems may be employed.

The first barrel 122 may be regarded as a container together with the closure 132, reciprocable

stopper 142, conduit and valve assembly 176, and cover 144 for storing, and subsequently mixing, the first component 140.

The second barrel 148 is preferably initially provided with a surrounding, protective sleeve 152 which is removed and discarded subsequent to use. The second barrel 148 preferably has a cylindrical barrel portion 150 containing a liquid second constituent 146 that is retained within the barrel portion 150 by a plunger assembly or plunger 164 which includes a stem or shank having a piston 168 at one end slidably disposed within the barrel portion 150 and having a thumb push flange at the other end.

The bottom end of the second barrel 148 defines a discharge end 156. The end 156 includes an outwardly projecting discharge conduit 158 (which is preferably in the form of a standard luer nozzle) defining an internal discharge passage 159 communicating through the discharge end 156 to accommodate the discharge of fluid from the barrel portion 150 of the second barrel 148. The conduit 158 accommodates fluid-tight connection with the female luer socket which defines the inlet 177A of the conduit assembly 176 in the first barrel 122.

An axially extending collar 161 is spaced from, and surrounds, the discharge conduit 158. The collar 161 defines an internal thread form of the type that is employed in connection systems marketed under the trademark LUER-LOK. Thus, the collar 161 can be threadingly engaged with the thread flange 179 at the inlet end of the conduit and valve assembly 176 which projects from the reciprocable stopper 142 in the first barrel 122. The second barrel projecting conduit 158 is adapted to enter into the inlet 177A of the conduit and valve assembly 176 to form a leak-tight seal with the

conduit 177. The second barrel collar 161 and conduit 158, and the first barrel conduit and valve assembly 176 thus function as a cooperating fluid transfer connector means or coupling means for connecting the second barrel 148 with the first barrel 122 first chamber 124 through the reciprocable stopper 142. Other suitable connection structures could be used in place of the specific form of the collar 161, conduit 158, and conduit and valve assembly 176 illustrated.

Preferably, a secondary, removable closure member 162, in the form of a threaded plug, is threadingly engaged with the collar 161, and it must be removed prior to use. This prevents ingress of contaminants and insures that the liquid second constituent will not leak out of the second barrel 148. Of course, even if the removable closure 162 is not employed, the liquid second constituent 146 cannot leak out of a small diameter passage 159 because there is no vent system that would admit ambient air into the second barrel 148 so as to permit the liquid constituent 146 to flow out solely under the influence of gravity.

The second barrel 148 may be regarded together with the closure member 162 and plunger 164 as a second container or syringe for holding, and subsequently discharging, the liquid second constituent 146.

To mix the two components, both barrels are preferably held in an inverted position. The closure 162 is removed from the second barrel 148. The second barrel 148 is inserted into the first barrel 122 to connect the second barrel discharge conduit 158 with the first barrel conduit assembly 176.

The second barrel luer nozzle conduit 158 is inserted into the female luer socket inlet 177A of the first barrel conduit and valve assembly 176. The thread

in the second barrel collar 161 is then engaged with the flange 179 on the first barrel conduit and valve assembly 176. Then relative rotation between the two barrels is effected to complete the threaded engagement.

Subsequently, the second barrel plunger 164 can be pushed toward the discharge passage 159. The liquid second constituent 146 flows from the second barrel 148 through the conduit and valve assembly 176 (where the valve member 187 opens) into the first barrel 122, and the reciprocable stopper 142 moves outwardly in the first barrel 122 along with the second barrel 148 connected to the assembly 176.

The first barrel 122 and second barrel 148 could also merely be pulled outwardly relative to each other while ambient air pressure acts on the exterior surface of the plunger piston 168 and is transferred to the liquid second constituent 146. As the stopper 142 is pulled outwardly, the volume beneath the stopper 142 within the first barrel chamber 124 increases while the pressure within the chamber 124 decreases. This results in a pressure differential which opens the valve member 187 as the liquid second constituent 146 flows into the first barrel 122 to combine with the first constituent 140.

As the liquid second constituent 146 is transferred to the first barrel 122, the outward movement of the two barrels 122 and 148 relative to each other is continued until the bottom interior surface of the plunger piston 168 engages the bottom, interior surface of the second barrel 148. At this point, all of the liquid second constituent 146 has been expelled from the barrel portion 150 of the second barrel 148 into the first barrel 122. The assembly can be shaken to ensure good mixing.

The first closure 132 can then be removed from the first barrel 122, and the delivery end 126 can be

connected to a suitable receiving component or discharge tubing (not illustrated). Alternatively, a needle, such as the needle 34 illustrated for the first embodiment in FIG. 5, may be attached to the first barrel 122.

Subsequently, the thumb push flange of the plunger 164 can be pushed inwardly to move the second barrel 148 and connected reciprocable stopper 142 inwardly further into the first barrel 122. This expels the combined constituents 140 and 146 from the first barrel 122.

It will be appreciated that the first barrel conduit and valve assembly 176, second barrel collar 161, and the second barrel conduit 158 cooperatively define a fluid transfer connector means or coupling means in the form of a flow-accommodating connection which permits the liquid second constituent 146 to flow from the second barrel 148 into the first barrel 122. This fluid transfer connector means or coupling means also accommodates the outward movement of the second barrel 148 relative to the first barrel 122 during the transfer of the liquid second constituent 146 from the second barrel 148 to the first barrel 122. Additionally, this fluid transfer connector means or coupling means accommodates the subsequent inward movement of the second barrel 148 during the dispensing of the combined constituents from the first chamber 124 of the first barrel 122.

The unique fluid transfer connector means or coupling means employed in the embodiment illustrated in FIGS. 6-9 may be characterized as including (1) a fluid communicating means, and (2) a cooperating connecting means.

The "fluid communicating means" includes (a) a "first fluid connector," preferably in the form of the luer-type socket or conduit 177 defining a flow passage

into the first barrel 122, and (b) a cooperating "second fluid connector" in the form of the luer-type nozzle or conduit 158 defining a flow passage out of the second barrel 148.

The "cooperating connecting means" may include a friction-fit connection of luer-type nozzle or conduit 158 with the luer-type socket or conduit 177. Preferably, however, the connecting means also includes the thread form on the second barrel collar 161 and the radial flange 179 on the conduit and valve assembly 176 in the first barrel 122 to cooperatively establish a threaded connection.

A third embodiment of the present invention, which includes a modified form of the conduit and valve assembly, is illustrated in FIGS. 10 and 10A. This embodiment includes a first barrel 222 defining a first chamber 224 in which a reciprocable stopper 242 is slidably disposed above a first constituent (not visible in FIGS. 10 and 10A). A conduit 277 is mounted in the reciprocable stopper 242 and extends through the reciprocable stopper 242. The conduit 277 defines an internal passage 278 and has an inlet 277A and an outlet 277B. At the inlet 277A, the conduit 277 defines a standard female luer socket from which extends a connector flange 279 which may be identical to the flange 179 described above with reference to the embodiment illustrated in FIGS. 6-9.

The bottom of the reciprocable stopper 242 has a frusto-conical shape 243 with a partial slit 289 oriented transversely to the axis of the frusto-conical shape at a outlet 277B of the conduit 277. This slit defines a flap or valve member 287 which is attached with an unslit portion 290 (FIG. 10A) to the main body of the stopper 242. The portion 290 is resilient and normally

biases the valve member 287 upwardly against the outlet 277B of the conduit 277 to occlude the passage 278.

The stopper 242 and conduit 277 illustrated in FIGS. 10 and 10A are adapted to cooperate with a second container or barrel (not illustrated) that can be identical to the second barrel 148 described above with reference to the second embodiment illustrated in FIG. 6. The second barrel can be inserted into the first barrel 222 and connected to the conduit 277 in the same manner as described above for the connection of the embodiment of the second barrel 148 with the first barrel 122 illustrated in FIG. 6. The operation of the embodiment of the system illustrated in FIGS. 10 and 10A with respect to combining the two constituents and subsequently dispensing them is identical with the operation of the second embodiment described above with reference to FIGS. 6-9.

A fourth embodiment of the syringe system is illustrated in FIGS. 11 and 12. A number of the elements of the fourth embodiment of the syringe system are identical or functionally analogous to corresponding elements in the first embodiment illustrated in FIGS. 1-5. The elements of the fourth embodiment illustrated in FIGS. 11 and 12 are designated by three digit reference numbers between 300 and 399. The last two digits of the fourth embodiment reference numbers for elements corresponding to elements in the first embodiment are identical to the last two digits of the reference numbers used to designate those corresponding elements in the first embodiment.

With reference to FIG. 11, the fourth embodiment of the syringe system includes a first barrel 322 which has a first chamber 324 containing a first constituent 340. The lower portion of the first barrel 322 includes a delivery end or dispensing end 326 defining a delivery passage or dispensing passage 328. Preferably, the

delivery passage 328 is occluded with a first, removable closure 332 which may be held in a friction fit on the delivery end 326. Other connection systems may be employed, such as snap-fit beads and grooves, threads, etc.

A reciprocable stopper 342 (which may be alternatively characterized as a moveable seal, grommet, or plunger piston) is provided above the first constituent 340 in the first chamber 324. The reciprocable stopper 342 has a lower end surface defining a conical shape 343. As shown in FIG. 11, the apex of the cone has at least one slit 389 (or two intersecting slits, not illustrated). The single slit 389 defines two lips or flaps 387. Two intersecting slits would define four lips. The lips 387 are normally biased to a closed position as illustrated in FIG. 11. The upper end of the reciprocable stopper 342 has an enlarged receiving cavity 393 and a smaller entrance passage 394 which together define a retention shoulder 395.

The reciprocable stopper 342 is initially installed in the first barrel 322 in a frictional engagement sufficient to prevent movement of the stopper during transport, storage, and handling.

The first barrel 322 may be regarded as a first container together with the reciprocable stopper 342 and closure 332 for storing the first constituent 340.

The reciprocable stopper 342 is adapted to be engaged, and moved, with a second barrel 348 which includes a cylindrical barrel portion 350 sized to be disposed in the first barrel 322.

The barrel portion 350 has a discharge end 356 defining a discharge passage 359 communicating through the discharge end 356 to accommodate the discharge of fluid from the barrel portion 350. The discharge end 356 has an

enlarged head 396 and a smaller neck 398 (FIG. 11). The neck 398 and head 396 together define a transverse shoulder 399.

A liquid second constituent 346 is contained within the barrel portion 350 below a plunger 364 which has a piston 368. Preferably, in order to minimize the likelihood of contaminant ingress and to minimize the likelihood of leakage of the constituent 346, a suitable closure 362 is removably mounted to the discharge end 356. The closure 362 may be held on the discharge end 356 by means of a friction fit or by other suitable conventional or special means, such as threads, snap-fit beads and grooves, etc.

The second barrel 348 may be characterized together with the closure 362 and plunger 364 as a second container or syringe for holding and storing the liquid second constituent 346 and subsequently discharging it.

Preferably, a protective sleeve (not illustrated) may be provided for surrounding the second barrel 348 in substantially the same manner that the sleeve 52 surrounds the second barrel 48 of the first embodiment illustrated in FIG. 1.

Also, if desired, the first barrel 322 may include a removable cover (not illustrated), such as the cover 44 shown on the top of the first barrel 22 of the first embodiment illustrated in FIG. 1.

In order to use the system illustrated in FIGS. 11 and 12, the closure 362 is removed from the second barrel 348. The second barrel 348 is then disposed within the first barrel 322. Preferably, this step is accomplished by first inverting the second barrel 348 before the closure 362 is removed. The first barrel 322 is also inverted, and the two barrels are telescopically engaged in the inverted position. The second barrel 348

is pushed into the first barrel 322 until the second barrel head 396 sufficiently expands the seal entrance passage 394 and enters into the seal receiving cavity 393. In this position, the second barrel dispensing end neck 398 is received in the smaller entrance passage 394 which, owing to the resiliency of the reciprocable stopper 342, has assumed its smaller diameter configuration whereby the seal retaining flange 395 engages the second container flange 399. This prevents separation of the second barrel 348 from the first barrel reciprocable stopper 342.

In the initially engaged position, wherein the second barrel discharge end 356 is connected to the first barrel reciprocable stopper 342, the stopper lips, flaps, or valve members 387 remain closed so as to ensure that there will be no leakage of the liquid second constituent into the first constituent 340.

Subsequently, the first and second barrels are moved outwardly relative to each other, as by pushing the second barrel plunger 364 to force the liquid second constituent 346 through the valve members 387 into the first barrel first chamber 324. This forces the second barrel 348 outwardly relative to the first barrel 322.

Alternatively, the two barrels 322 and 348 may be pulled apart. Ambient air pressure acting on the plunger 368 results in the liquid second constituent 346 in the second barrel 348 being maintained under the ambient atmospheric pressure. The increasing volume of the first chamber 324 under the reciprocable stopper 342 creates a negative pressure differential, and the liquid second constituent 346 forces the valve members 387 outwardly to the open position illustrated in FIG. 12. The liquid second constituent 346 can thus flow into the first constituent 340.

The two barrels move outwardly relative to each other until the bottom surface of the plunger piston 368 engages the bottom of the cylindrical barrel portion 350 of the second barrel 348. At this point, all of the liquid second constituent 346 has been expelled into the first constituent 340 in the first chamber 324. The valve lips 387 then close. The assembly can then be shaken to ensure good mixing.

Subsequently, the closure 332 is removed from the first barrel delivery end 326. The first barrel delivery end 326 can then be connected to a receiving component or discharge tubing (not illustrated) or to a hypodermic needle (such as the needle 34 described above with reference to the first embodiment illustrated in FIGS. 1-5). Then the plunger 364 and second barrel 348 are pushed inwardly. This urges the plunger piston 368 against the bottom of the cylindrical barrel portion 350 of the second barrel 348 to move the second barrel 348 and connected reciprocable stopper 342 toward the bottom of the first container 322. This results in the combined constituents being dispensed from the first container 322.

A fifth embodiment of a syringe system, incorporating a design that may be preferred in some applications, is illustrated in FIGS. 13-16. A number of the elements of the fifth embodiment of the syringe system are identical or functionally analogous to corresponding elements in the first four embodiments illustrated in FIGS. 1-12. The elements of the fifth embodiment illustrated in FIGS. 13-16 are designated by three digit reference numbers between 400 and 499. The last two digits of the fifth embodiment reference numbers for elements corresponding to elements in the first and fourth embodiments are identical with the last two digit

reference numbers used to designate those corresponding elements in the first and fourth embodiments.

With reference to FIG. 13, the preferred form of the syringe system includes a first barrel 422 which has a first chamber 424 containing a first constituent 440. The lower portion of the first barrel 422 includes a delivery end or dispensing end 426 defining a delivery passage or dispensing passage 428. Preferably, the delivery passage 428 is occluded with a first, removable closure 432 which may be held in a threaded engagement on the delivery end 426. To this end, the first barrel delivery end 426 includes a tapered luer fitment 433 surrounded by an annular collar 435 defining an interior, female thread form 436. The closure 432 includes a stem 437 for being received in the delivery passage 428 and has an exterior flange or lug 438 for engaging the female thread form 436.

A reciprocable stopper 442 is provided above the first constituent 440 in the first chamber 424. The reciprocable stopper 442 may alternatively be characterized as a moveable seal, grommet, or plunger piston. The reciprocable stopper 442 has a lower end defining an inner side or end surface 443 which has a conical shape. The apex of the cone has one slit 489. The slit 489 defines two lips or flaps 487 that are normally biased to a closed position as illustrated in solid line in FIG. 15.

The reciprocable stopper 442 has an outer side or upper end surface 439. Between the stopper outer side surface 439 and the stopper inner side surface 443 there is an enlarged receiving cavity 493 and a smaller entrance passage 494 which together define a retention shoulder 495.

The reciprocable stopper 442 is initially installed in the first barrel 422 in a frictional engagement sufficient to prevent movement of the stopper during transport, storage, and handling. The reciprocable stopper 442 is adapted to receive a support member 441.

The support member 441 defines a flow passage 445 and a communicating luer socket 444 which can receive a luer nozzle (as described hereinafter). The support member 441 has an enlarged head 496 and a smaller neck 498 (FIG. 14). The neck 498 and head 496 together define a transverse shoulder 499.

The support member 441 can be pushed into the resilient, reciprocable stopper 442 until the support member head 496 sufficiently expands the seal entrance passage 494 and enters into the seal receiving cavity 493. In this position, the support member neck 498 is received in the smaller entrance passage 494 which, owing to the resiliency of the reciprocable stopper 442, has assumed its smaller diameter configuration whereby the reciprocable stopper retaining flange 495 engages the support member shoulder 499. This prevents separation of the support member 441 from the first barrel reciprocable stopper 442. The member 441 also preferably has a support flange 457 (FIG. 14). This prevents the reciprocable stopper 442 from being deformed to the extent that it might leak.

The first barrel 422 may be characterized together with the reciprocable stopper 442, support member 441, and closure 432 as a first container for storing the first constituent 440 and for subsequently mixing it with a liquid second constituent 446 contained in a second barrel 448 (FIG. 13).

With reference to FIG. 13, the liquid second constituent 446 is contained within the cylindrical barrel

portion 450 of the second barrel 448 below a plunger 464 which has a piston 468. The barrel 448 has a lower discharge end 456 defining a discharge passage 459. The discharge end 456 preferably has the configuration of a luer-type nozzle for being received in the luer-type socket 444 of the support member 441.

Preferably, in order to minimize the likelihood of contaminant ingress and to minimize the likelihood of leakage of the constituent 446, a suitable closure 462 is removably mounted to the discharge end 456. The closure 462 may be held on the discharge end 456 by means of a friction fit or by other suitable conventional or special means, such as threads, snap-fit beads and grooves, etc.

The second barrel 448 together with the closure 462 and plunger 464 may be characterized as a second container or syringe for storing and subsequently discharging the liquid second constituent 446.

Preferably, a protective sleeve (not illustrated) may be provided for surrounding the second barrel 448 in substantially the same manner that the sleeve 52 surrounds the second barrel 48 of the first embodiment illustrated in FIG. 1.

Also, if desired, the first barrel 422 may include a removable cover (not illustrated), such as the cover 44 shown on the top of the first barrel 22 of the first embodiment illustrated in FIG. 1.

In order to use the system illustrated in FIGS. 13-16, the cap 462 is removed from the second barrel 448. The second barrel 448 is then disposed within the first barrel 422. Preferably, this step is accomplished by first inverting the second barrel 448 before the closure 462 is removed. The first barrel 422 is also inverted, and the two barrels are telescopically engaged in the inverted position.

The luer-type nozzle at the discharge end 456 of the second barrel 448 is disposed within the luer-type socket 444 of the support member 441. This may be a friction fit connection. Alternatively, a more positive mechanical connection could be employed as discussed hereinafter with respect to the sixth embodiment shown in FIG. 17.

In the installed position, wherein the second barrel discharge end 456 is mounted via the member 441 to the first barrel reciprocable stopper 442, the stopper flaps, lips, or valve members 487 remain closed so as to ensure that there will be no leakage of the liquid second constituent into the first constituent 440.

The plunger 464 can be pushed to discharge the liquid second constituent 446 through the reciprocable stopper slit 489 into the first chamber 424 of the first barrel 422. As the second constituent 446 flows into the first barrel chamber 424, the reciprocable stopper 442 and second barrel 448 move outwardly. Alternatively, the first and second barrels 422 and 448 can be pulled outwardly relative to each other. Ambient air pressure acting on the plunger piston 468 results in the liquid second constituent 446 being maintained under the ambient atmospheric pressure. The increasing volume of the first chamber 424 under the reciprocable stopper 442 creates a negative pressure differential, and the liquid second constituent 446 forces the stopper lips or valve members 487 outwardly to the open position illustrated in FIG. 14. The liquid second constituent 446 can thus flow into the first constituent 440.

The two barrels 422 and 448 move outwardly relative to each other until the bottom surface of the plunger piston 468 engages the bottom of the cylindrical barrel portion 450 of the second barrel 448. At this

point, all of the liquid second constituent 446 has been expelled into the first constituent 440 in the first chamber 424. The valve flaps 487 then close. The assembly can then be shaken to ensure good mixing.

Subsequently, the closure 432 is removed from the first barrel delivery end 426. The first barrel delivery end 426 can then be connected to a receiving component or discharge tubing (not illustrated) or to a hypodermic needle (such as the needle 34 described above with reference to the first embodiment illustrated in FIGS. 1-5). Then the plunger 464 is pushed inwardly. This urges the piston 468 against the bottom of the cylindrical barrel portion 450 of the second barrel 448 to move the second barrel 422, support member 441, and connected reciprocable stopper 442 toward the bottom of the first container 422. This results in the combined constituents being dispensed from the first barrel 422.

FIG. 17 illustrates a sixth embodiment of the present invention. The sixth embodiment is a modification of the fifth embodiment described above with reference to FIGS. 13-16.

In particular, the sixth embodiment includes a support member 441A generally similar to the fifth embodiment support member 441. However, the support member 441A includes an upwardly extending skirt 451A which has an internal, female thread form 453A.

A second barrel 448A is provided with a configuration generally similar to that of the fifth embodiment second barrel 448 except that the sixth embodiment second barrel 448A includes a radial lug, flange, or thread form 455A to threadingly engage the support member thread form 453A. This provides a positive mechanical connection between the second barrel 448A and the support member 441A.

In each of the fourth, fifth, and sixth embodiments illustrated in FIGS. 11-17, it is preferable to provide a clearance between the end of the head 496 of the support member 441 and the closed stopper valve lips or flaps (e.g., 487 in FIG. 16) when the stopper lips or flaps are closed. This insures that the stopper can properly collapse as far as necessary to close the slit.

The embodiments illustrated in FIGS. 11-17 may be characterized as employing a unique fluid transfer connector means or coupling means. The fluid transfer connector means or coupling means may be characterized as including (1) fluid communicating means, and (2) cooperating connecting means.

In the embodiment illustrated in FIGS. 11 and 12, the fluid communicating means include a first fluid connector in the form of a passage 359 in the second barrel discharge end 356 and a second fluid connector in the form of the flow path through the reciprocable stopper 342 and stopper flaps or lips 387. The cooperating connecting means include the enlarged head 396 on the second barrel 348 and the cooperating stopper receiving cavity 393 and retention shoulder 395.

In the embodiments illustrated in FIGS. 13-17, the fluid communicating means includes the flow passage through the reciprocable stopper 442 as well as a first fluid connector in the form of the luer-type socket or conduit 444 (FIG. 14) defining a flow passage in the support member 441 and a cooperating second fluid connector in the form of the luer-type nozzle 456 defining a flow passage in the second barrel 448. The cooperating connecting means may include just a friction-fit connection of luer-type nozzle 456 in the luer-type socket 444 as well as the engagement between the support member 441 and stopper 442. Preferably, however, as shown in

FIG. 17, the connecting means also includes the thread form 453A on the support member 441A and the radial flange 455A on the second barrel 448A which cooperatively establish a threaded connection.

It will be appreciated that, in all of the embodiments illustrated, the dispensing ends or delivery ends of the first barrels are sealed with removable closures (such as the first container dispensing end closure 32). The second barrel discharge end may include a closure (i.e., closure 62 illustrated in FIG. 1). Further, such closures, if employed, may be provided in alternate forms such as threadable elastomeric seal members, flexible adhesive seal members, shrink wrap films, or other closure systems.

The above-described syringe system of the present invention provides an advantageous means for dispensing a combination of two constituents that must be kept separate from each other until they are to be used in combination. The system is self-contained and sealed. Reconstitution or dilution of a drug using this system can be effected at bedside when the drug is needed. The choice of the diluent liquid is not restricted or limited because the system accommodates any diluent compatible with the structural materials employed.

The system permits the constituents to be stored in forms in which the stability of the components is maximized. Because the reconstituted product is used immediately, provisions do not have to be made for refrigeration or other storage procedures which might otherwise be required for certain types of reconstituted products.

It will be readily apparent from the foregoing detailed description of the invention and from the illustrations thereof that numerous variations and

modifications may be effected without departing from the true spirit and scope of the novel concepts or principles of this invention.

WHAT IS CLAIMED IS:

1. A syringe mixing and delivery system comprising:

a first barrel having an open end and an opposite delivery end defining a delivery passage;

a reciprocable stopper sealingly disposed in said first barrel to define a first chamber between said delivery passage and said reciprocable stopper for containing a first constituent in said first chamber;

a second barrel that is sized to be disposed in said first barrel and that has an open end and an opposite discharge end defining a discharge passage;

a slidable plunger sealingly disposed within said second barrel to define a second chamber between said discharge passage and said slidable plunger for containing a liquid second constituent in said second chamber; and

fluid transfer connector means for operatively connecting said second barrel with said reciprocable stopper to permit flow of said liquid second constituent through said stopper from said second chamber to said first chamber to mix with said first constituent when said second barrel discharge end and plunger are moved closer together whereby subsequent movement of said second barrel and reciprocable stopper together toward said delivery passage of said first barrel expresses the mixed constituents out of said first chamber through said delivery passage.

2. The system in accordance with claim 1 wherein said fluid transfer connector means includes:

(1) a hollow piercing needle carried by said second barrel in communication with said discharge passage; and

(2) a portion of said reciprocable stopper being fully penetratable by said piercing needle.

3. The system in accordance with claim 1 wherein said fluid transfer connector means includes:

(1) a conduit extending through said reciprocable stopper and having an inlet end and an outlet end;

(2) a flapper valve member in said reciprocable stopper adjacent said conduit outlet end and biased to a normally closed position occluding said conduit to said conduit outlet end;

(3) a flange on said conduit inlet end; and

(4) a thread form on said second barrel for being threadingly engaged by said flange whereby fluid communication is established between said discharge passage and said conduit.

4. The system in accordance with claim 1 wherein said fluid transfer connector means includes:

(1) a resilient portion defined in said reciprocable stopper and which has at least one longitudinal slit therethrough defining resilient lips which are biased to a normally closed position and which can open toward said delivery passage into said first chamber;

(2) an enlarged receiving cavity in said reciprocable stopper resilient portion adjacent said resilient lips and a smaller entrance passage in said reciprocable stopper opening into said enlarged cavity whereby a retention shoulder is defined at one end of said enlarged cavity around said smaller entrance passage; and

(3) an enlarged head at said discharge passage of said second barrel for being received in said

enlarged receiving cavity of said reciprocable stopper and a smaller neck at said discharge passage of said second barrel for being received in said entrance passage of said reciprocable stopper whereby said discharge passage of said second barrel is normally occluded by said biased closed resilient lips of said reciprocable stopper.

5. The system in accordance with claim 1 wherein said fluid transfer connector means includes (a) connecting means for connecting said second barrel with said reciprocable stopper, and (b) fluid communicating means permitting flow of said liquid second constituent through said stopper from said second chamber to said first chamber, said fluid communicating means comprising:

a first fluid connector associated with said reciprocable stopper in said first barrel;

a cooperating second fluid connector associated with said discharge passage of said second barrel; and

a fluid passageway from said first fluid connector to said first chamber including a normally closed one way flow valve.

6. The system in accordance with claim 5 wherein

said fluid passageway is defined at least in part through said reciprocable stopper; and

said one way flow valve is integral with said reciprocal stopper.

7. The system in accordance with claim 6 wherein

said first fluid connector includes a luer socket mounted in said reciprocable stopper in fluid communication with said one way flow valve;

said second flow connector includes a luer nozzle at said discharge passage of said second barrel; and

said connecting means comprises a thread form on said second barrel proximate said luer nozzle and a radial flange on said luer socket, said radial flange being threadably engageable with said second barrel thread form for connecting said luer nozzle to said luer socket.

8. The system in accordance with claim 5 in which

said first fluid connector is a support member having a luer socket that is in fluid communication with said fluid passageway;

said cooperating second fluid connector is a luer nozzle at said discharge end of said second barrel for being placed in fluid communication with said support member luer socket; and

said connecting means comprises a friction fit of said second barrel luer nozzle in said support member luer socket.

9. The system in accordance with claim 8 in which said connecting means further comprises a thread form defined in said support member proximate said luer socket and a radial flange on said second barrel for threadingly engaging said support member thread form.

10. The system in accordance with claim 1 wherein

said plunger includes a slidable piston and a shank removably mounted to said slidable piston; and

said system further includes

a first removable closure occluding said first barrel delivery passage;

a second removable closure occluding said second barrel discharge passage; and

a cover removably mounted to said open end of said first barrel opposite said delivery passage.

11. A prefilled syringe system for separately storing a first constituent and a liquid second constituent and for subsequently mixing and dispensing a mixture of said constituents, said system comprising:

a first barrel having an open end and an opposite delivery end defining a delivery passage;

a first removable closure sealingly occluding said delivery passage;

a reciprocable stopper sealingly disposed in said first barrel to define a first chamber between said delivery passage and said reciprocable stopper for containing a first constituent in said first chamber;

a second barrel that is sized to be disposed in said first barrel and that has an open end and a discharge end defining a discharge passage;

a second removable closure occluding said discharge passage;

a slidable plunger sealingly disposed within said second barrel to define a second chamber between said discharge passage and said slidable plunger for containing a liquid second constituent in said second chamber; and

coupling means for operatively coupling said second barrel to said reciprocable stopper in said first barrel when said second barrel is telescopically positioned in said open end of said first barrel so that said liquid second constituent can be caused to flow through said stopper from said second chamber to said

first chamber to mix with said first constituent by movement of said second barrel discharge end and plunger closer together whereby subsequent movement of said second barrel and reciprocable stopper together toward said delivery passage of said first barrel expresses the mixed constituents out of said first chamber through said delivery passage.

12. The prefilled syringe system in accordance with claim 11 in which said coupling means includes:

(1) a hollow piercing needle carried by said second barrel at said discharge passage and in fluid communication with said second chamber, and

(2) a portion of said reciprocable stopper being fully penetratable by, and couplingly engageable by, said piercing needle upon removal of said second removable closure from said discharge passage of said second barrel.

13. The prefilled syringe system in accordance with claim 11 wherein said coupling means comprises

(1) fluid communicating means for communicating fluid from said second chamber to said first chamber, and

(2) connecting means for connecting said second barrel with said reciprocable stopper.

14. The prefilled syringe system in accordance with claim 13 in which said fluid communicating means includes

(1) a conduit through said reciprocable stopper and having an inlet end and an outlet end;

(2) a valve member in said reciprocable stopper adjacent said conduit outlet end and biased to a

normally closed position occluding said conduit outlet end;

(3) a first fluid connector on said conduit inlet end; and

(4) a cooperating second fluid connector at said discharge passage of said second barrel for engaging said first fluid connector on said conduit inlet end upon removal of said second removable closure whereby fluid communication is established between said discharge passage and said conduit.

15. The prefilled syringe system in accordance with claim 14 wherein said connecting means includes a threadable flange on said first fluid connector at said conduit inlet end and a thread form on said second barrel on said cooperating second fluid connector at said discharge passage of said second barrel for being threadingly engaged by said threadable flange.

16. The prefilled syringe in accordance with claim 13 wherein

said fluid communicating means includes a resilient portion defined in said reciprocable stopper which has at least one longitudinal slit therethrough defining resilient lips which are biased to a normally closed position and which can open toward said delivery passage into said first chamber; and

said connecting means includes:

(1) an enlarged receiving cavity in said reciprocable stopper resilient portion adjacent said resilient lips and a smaller entrance passage in said reciprocable stopper opening into said enlarged cavity whereby a retention shoulder is defined at one end of said enlarged cavity around said entrance passage; and

(2) an enlarged head at said discharge passage of said second barrel received in said enlarged receiving cavity of said reciprocable stopper upon removal of said second removable closure and a smaller neck at said discharge passage of said second barrel for being received in said entrance passage of said reciprocable stopper whereby said discharge passage of said second barrel is normally occluded by said resilient lips of said reciprocable stopper in the biased closed position.

17. The prefilled syringe system in accordance with claim 11 wherein said coupling means includes

(a) a connecting means for connecting said second barrel with said reciprocable stopper, and

(b) a fluid communicating means for accommodating transfer of fluid from said second chamber to said first chamber, said fluid communicating means comprising:

a first fluid connector associated with said reciprocable stopper;

a cooperating second fluid connector associated with said discharge passage of said second barrel; and

an openable and closeable fluid passageway from said first fluid connector in said reciprocable stopper to said first chamber of said first barrel.

18. The prefilled syringe system in accordance with claim 17 wherein

said first fluid connector includes a stopper support member having a luer socket that is in fluid communication with said fluid passageway; and

said cooperating second fluid connector includes a luer nozzle at said discharge passage of said second

barrel for being placed in fluid communication with said support member.

19. The prefilled system in accordance with claim 18 wherein said fluid communicating means further comprises a resilient central portion defined in said reciprocable stopper which has at least one longitudinal slit therethrough defining resilient lips which are biased to a normally closed position and which can open toward said delivery passage into said first chamber to define at least a portion of said fluid passageway.

20. The prefilled syringe system in accordance with claim 19 wherein said connecting means includes

an enlarged receiving cavity in said reciprocable stopper central portion adjacent said resilient lips and a smaller entrance passage in said reciprocable stopper opening into said enlarged cavity whereby a retention shoulder is defined at one end of said enlarged cavity around said smaller entrance passage;

an enlarged head that is defined by said support member and that is received in said enlarged receiving cavity of said reciprocable stopper; and

a smaller neck that is defined by said support member and that is received in said entrance passage of said reciprocable stopper wherein said fluid passageway extends through said enlarged head and smaller neck from said luer socket through said longitudinal slit whereby said discharge passage of said second barrel is normally occluded by said biased closed resilient lips of said reciprocable stopper.

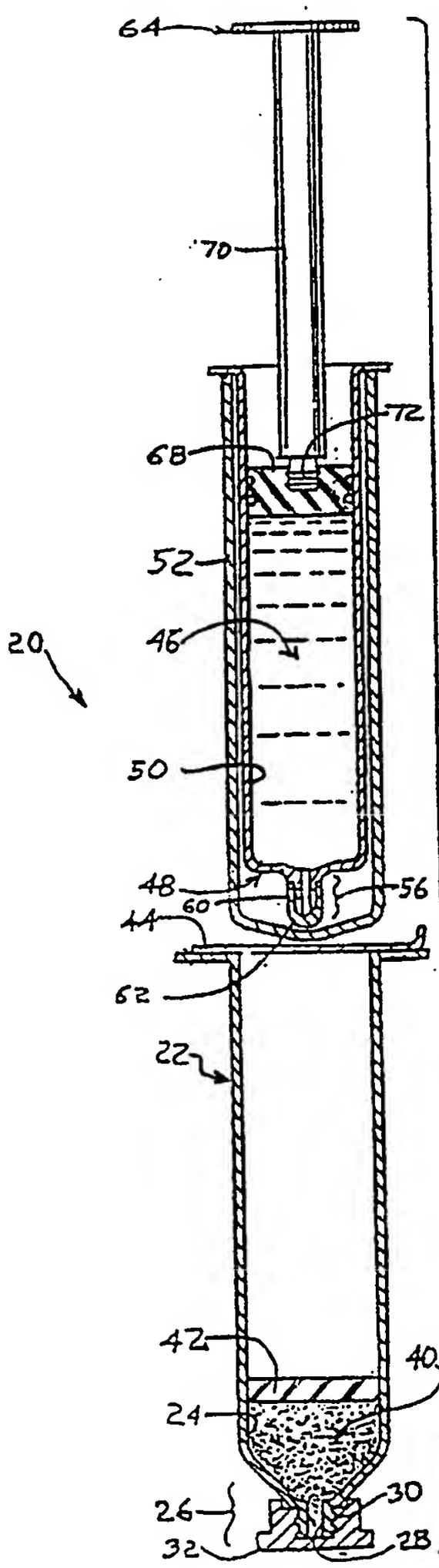

FIG. 1

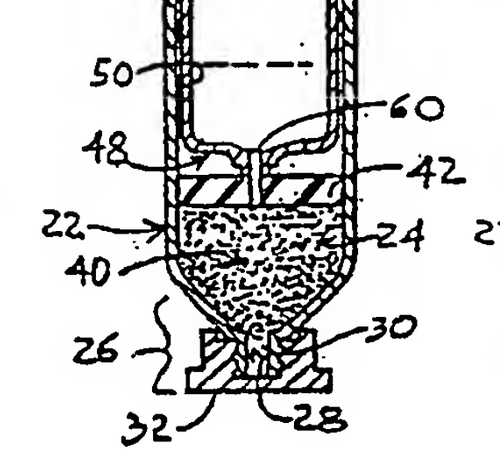

FIG. 3

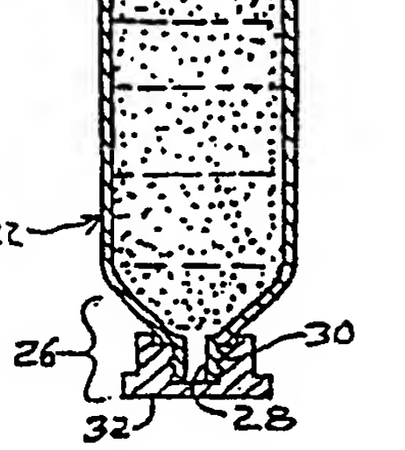

FIG. 4

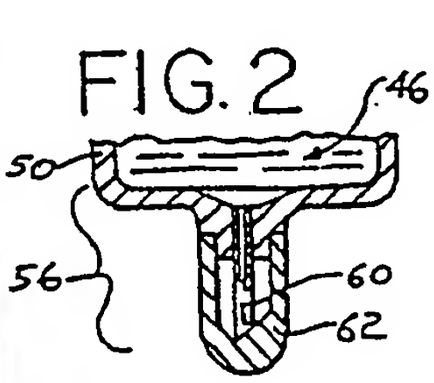

FIG. 2

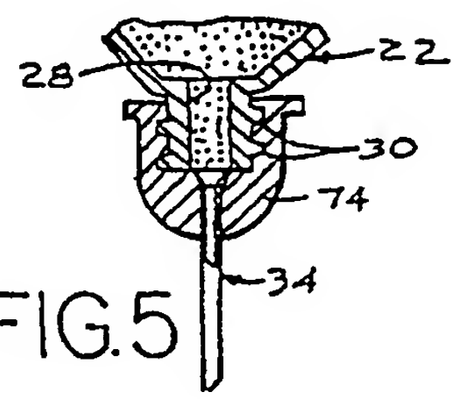

FIG. 5

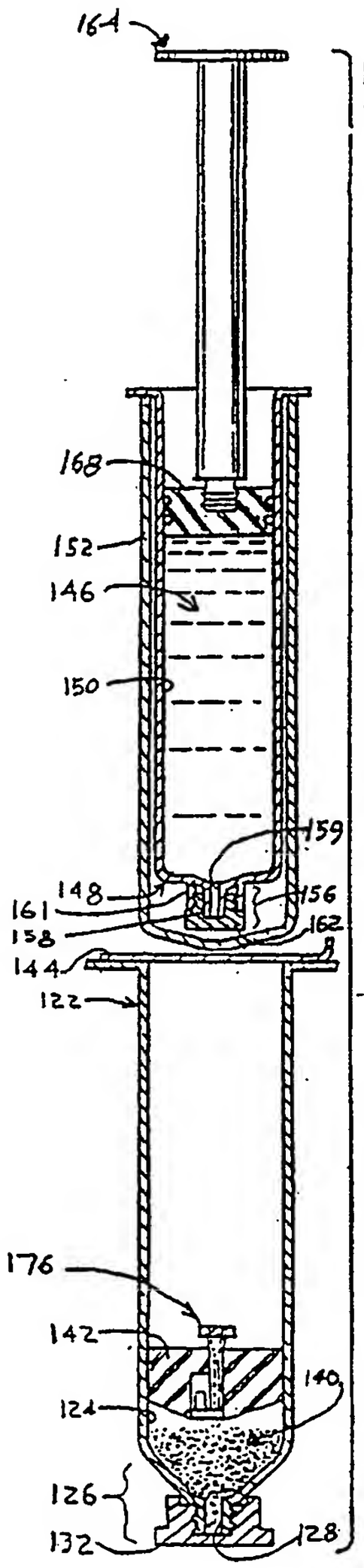

FIG. 6

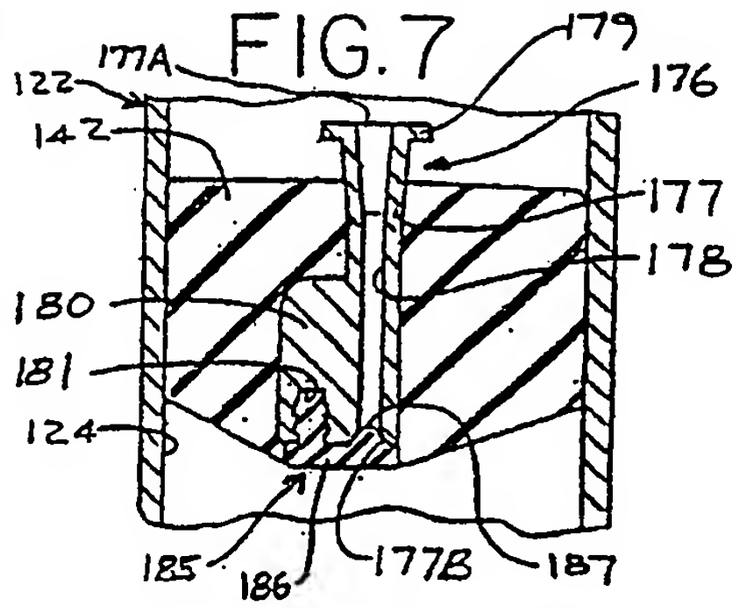

FIG. 7

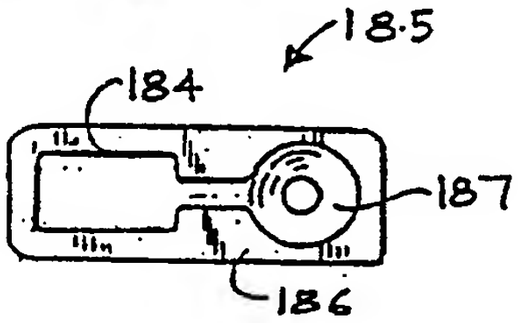

FIG. 9

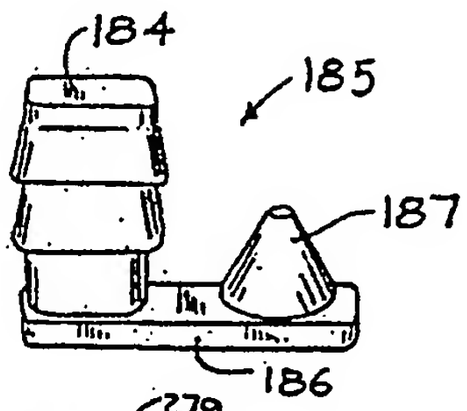

FIG. 8

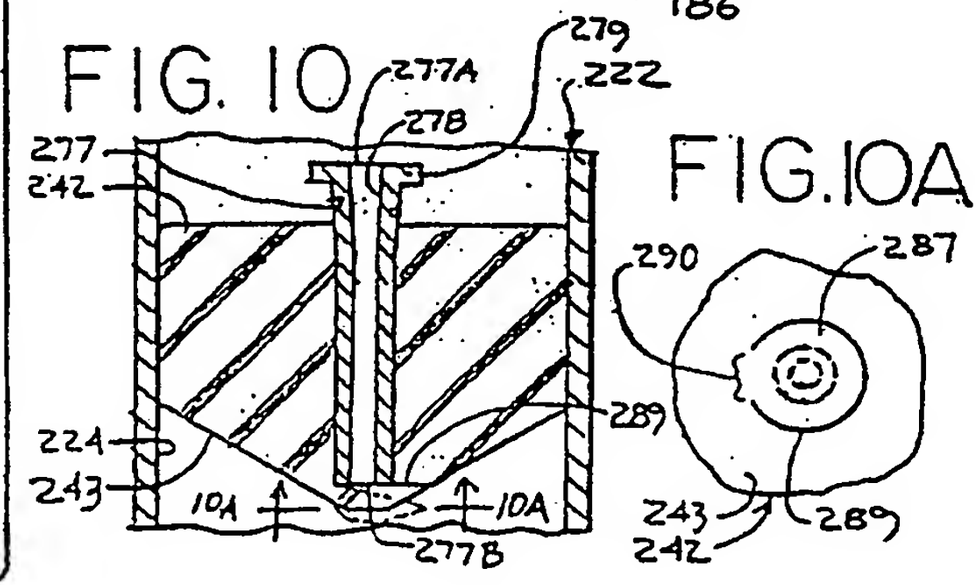

FIG. 10

FIG. 10A

FIG. 11

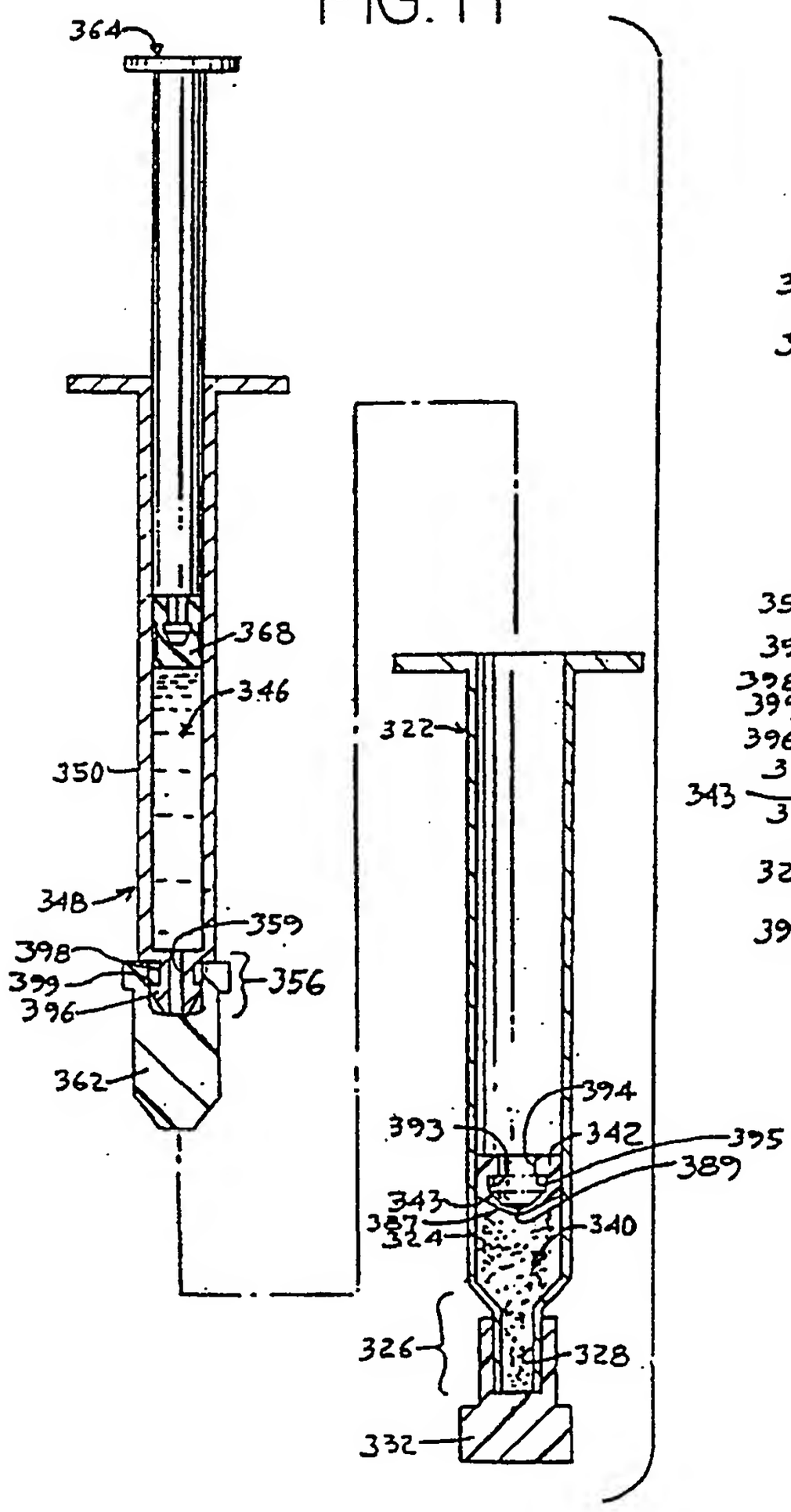
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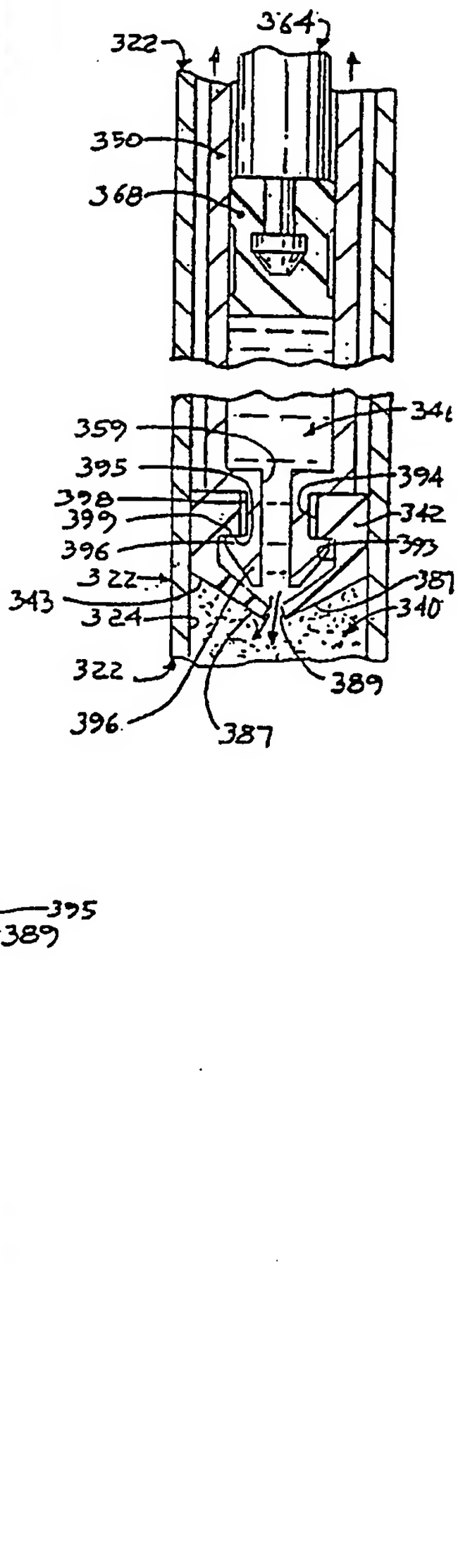
FIG. 12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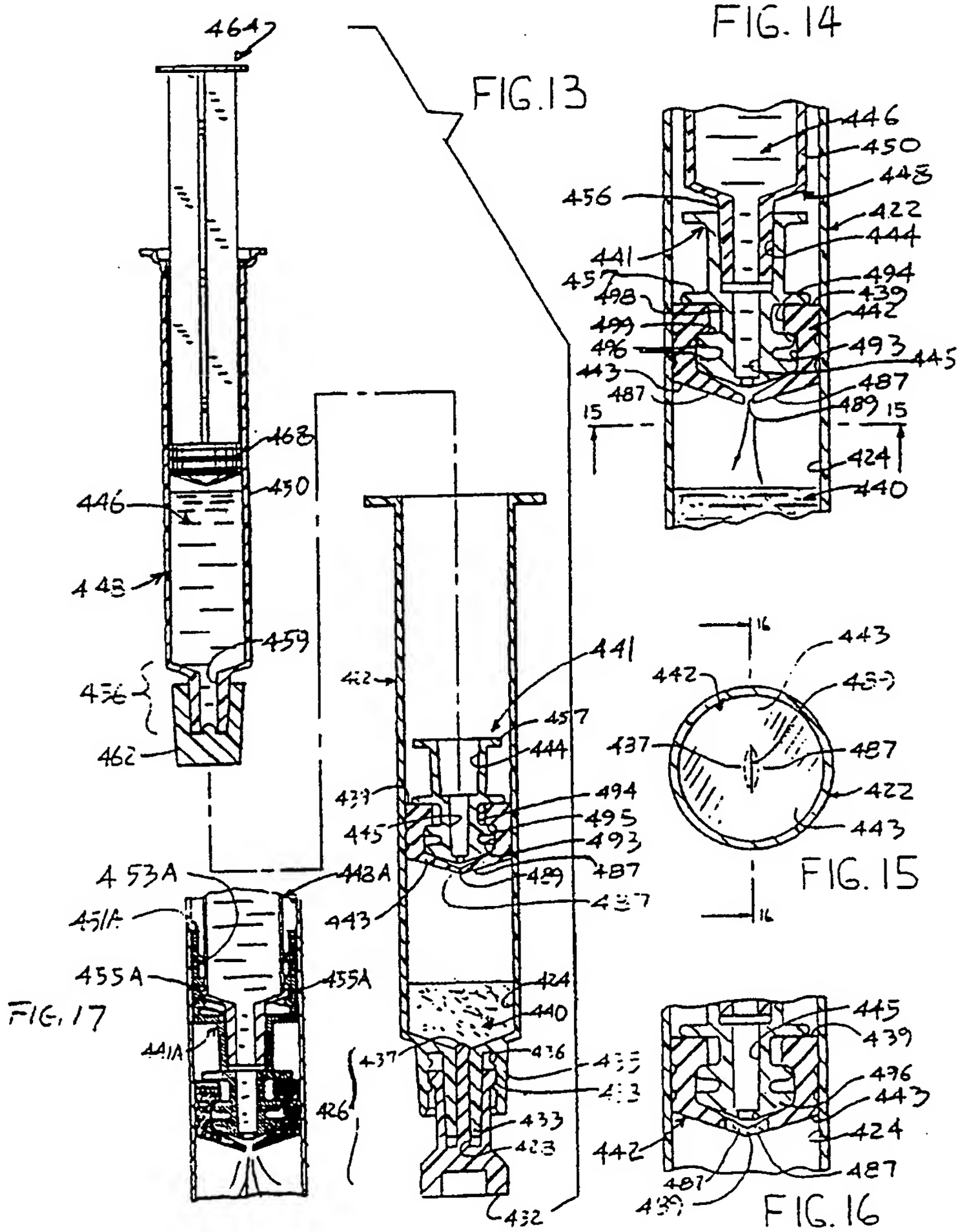

FIG. 13

FIG. 14

FIG. 15

FIG. 16

FIG. 17

INTERNATIONAL SEARCH REPORT

Inte. .ional Application No
PCT/US 97/17194

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M5/315

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 29106 A (ABOTT LABORATORIES) 26 September 1996 see page 11, line 11 - page 13, line 16 see page 14, line 24 - page 15, line 4 see page 16, line 3 - line 12 see figures 1-15	1,2,4-9, 11-20
Y	---	10
X	US 4 581 016 A (GETTIG) 8 April 1986 see the whole document	1,2
A	---	5,7,8,11
Y	US 4 581 023 A (KUNTZ) 8 April 1986 see column 4, line 53 - line 58; figure 3	10
A	---	3
	US 5 181 909 A (MCFARLANE) 26 January 1993 see column 2, line 47 - line 51; figures 1,2	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

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Date of the actual completion of theinternational search	Date of mailing of the international search report
26 January 1998	12/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sedy, R

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	US 5 569 193 A (HOFSTETTER ET AL.) 29 October 1996 cited in the application see the whole document	1-20
X,P	WO 96 30066 A (ABOTT LABORATORIES) 3 October 1996 see the whole document	1,2,4-9, 11-20

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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